Paid Circulation, 32,593

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Annual Meeting
Hotel Statler, Boston
May 17, 18, 19

The New England Journal of Medicine

FORMERLY THE BOSTON MEDICAL AND SURGICAL JOURNAL — *Established 1828*

VOLUME 252 • APRIL 7, 1955 • NUMBER 14

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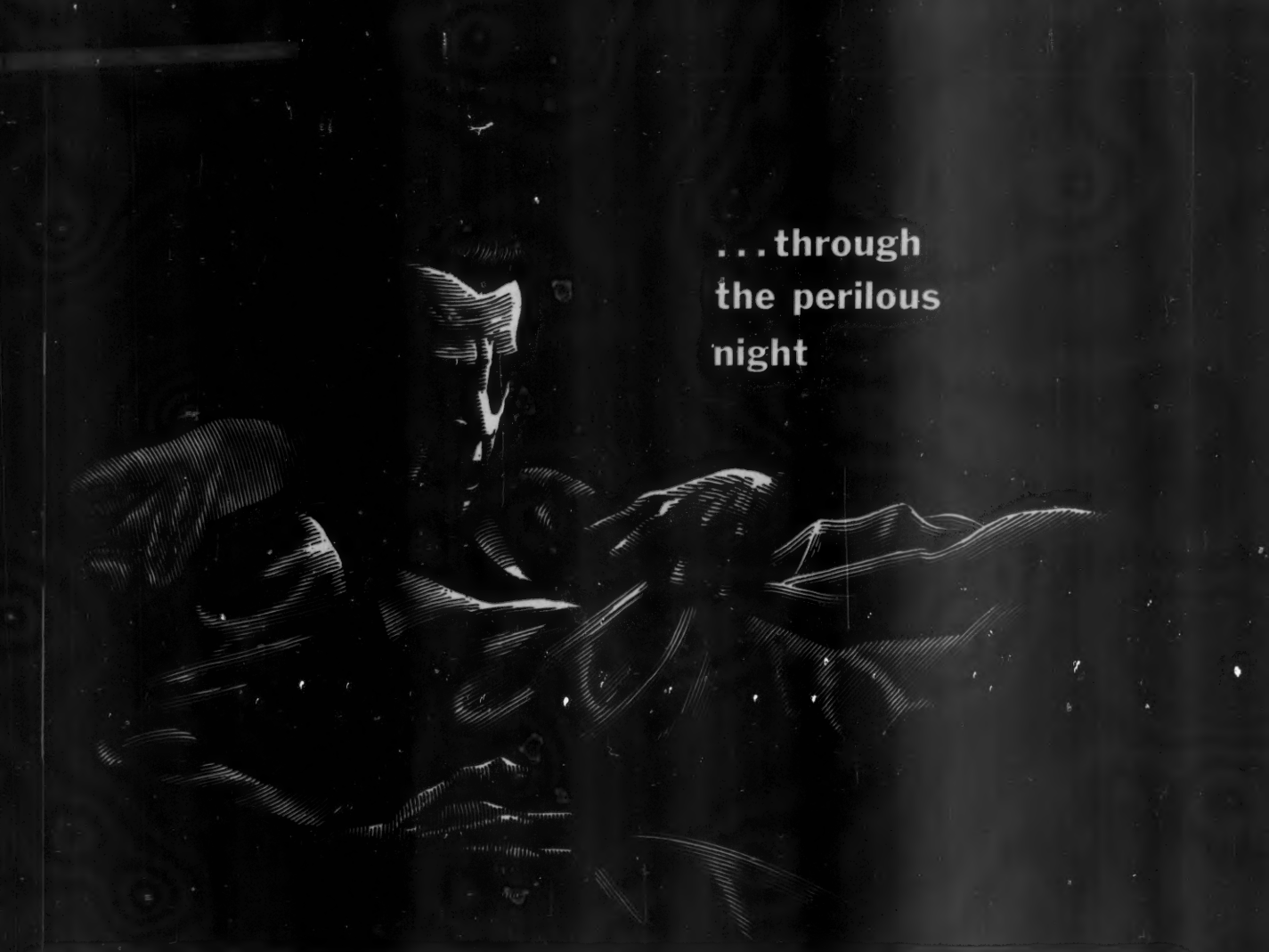

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1. Winsor, T., and Humphreys, P.: Angiology *3*:1 (Feb.) 1952. 2. Plotz, M.: New York State J. Med. *52*:2012 (Aug. 15) 1952. 3. Dailheu-Geoffroy, P.: L'Ouest-Médical, vol. 3 (July) 1950.

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*Neuhauser, I.: Successful Treatment of Intestinal Moniliasis with Fatty Acid-Resin Complex. A. M. A. Arch. Int. Med. 93:53, 1954. McGivney, J.: The Anorectal Complications of Broad Spectrum Antibiotic Therapy. Texas State Journal of Medicine. Jan. 1955.

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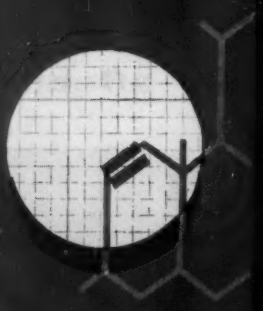

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1. DE POORTER, D.: BRUXELLES-MED. 34:1010 (JUNE 7) 1954

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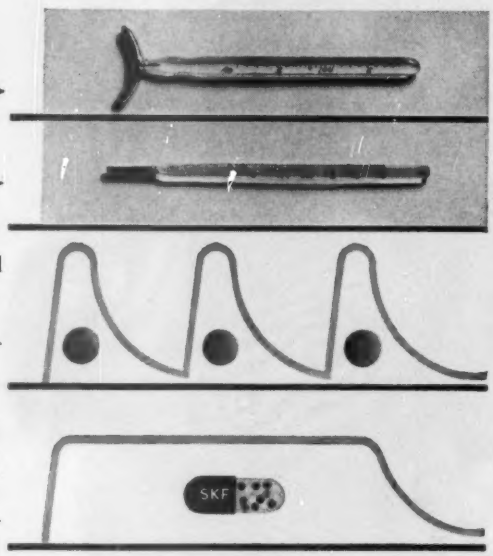

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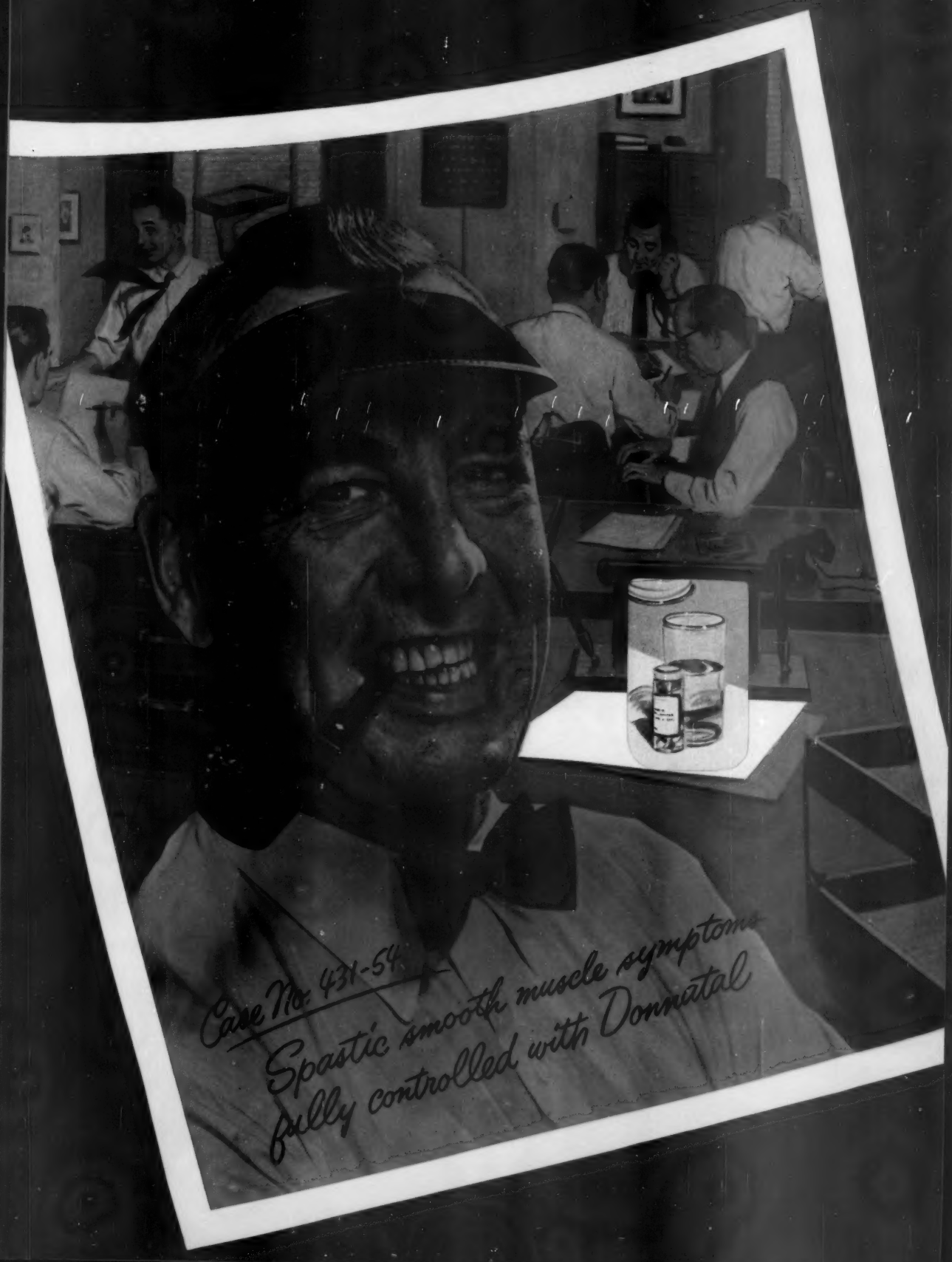

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†Seidmon, E. E. P., and Schaffer, N.: Ann. Allergy *18*:36, 1954.

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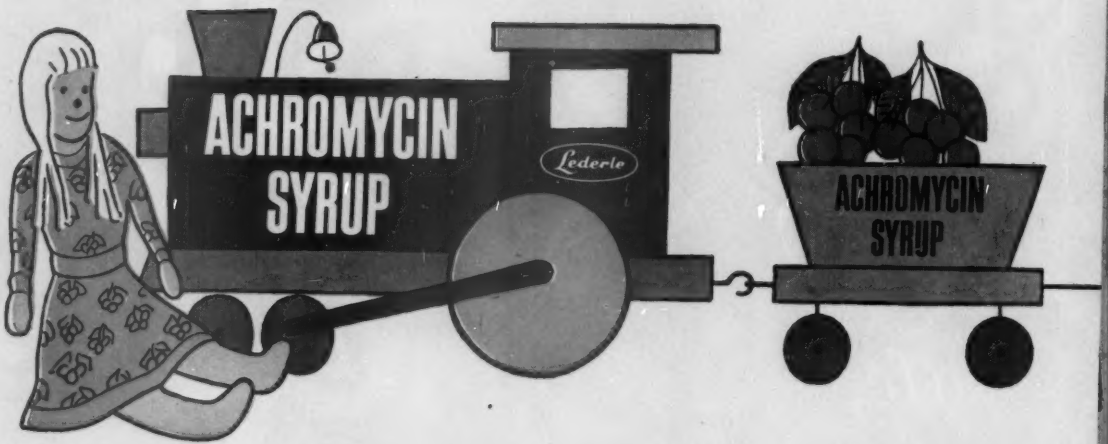

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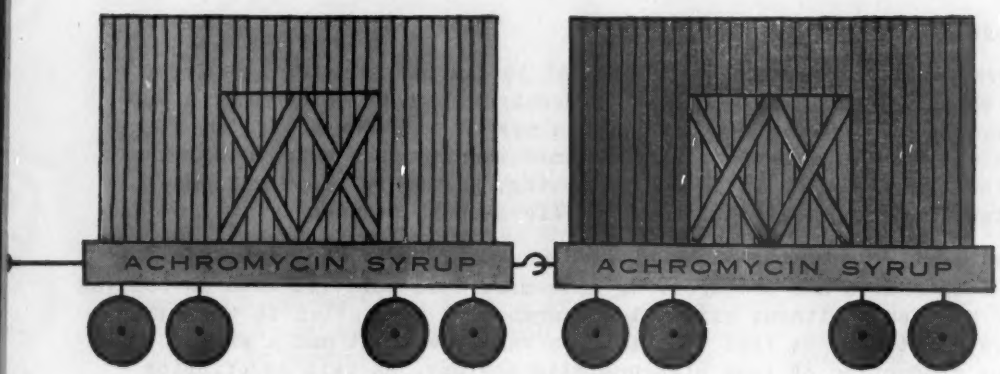

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The New England
Journal of Medicine

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Volume 252 APRIL 7, 1955 Number 14

MATERNAL HYDRAMNIOS AND CONGENITAL ANOMALIES OF THE CENTRAL NERVOUS SYSTEM*

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BOSTON

THE association of hydramnios with congenital anomalies, long recognized, was confirmed once again by a previous investigation into antecedent (prenatal) factors influencing tracheoesophageal fistula; hydramnios was present in 20 of the 107 cases.[1] The meaning of this association was obscure, and clarification is now sought reversing the approach by studying the results of 145 pregnancies complicated by hydramnios. These pregnancies terminated in the delivery of 68 defective infants, including 45 with anencephalus, 8 with spina bifida, 6 with hydrocephalus and 4 with mongolism.

THE GROUP STUDIED

The patients studied were for the most part residents of Boston; some came from the larger metropolitan district, and a few from other towns and cities in Massachusetts. All records of patients with a final diagnosis of hydramnios were used for computing the incidence of the disease at the Boston Lying-in Hospital for the years 1923-1949, inclusive; and the records of 145 patients with this diagnosis delivered from January 1, 1935, through June 30, 1950, were subjected to more exhaustive analysis. Clinical descriptions were not complete in all respects; therefore, in each section of this report the stated number of records used does not regularly total 145.

Diagnosis of hydramnios was by clinical criteria: a disproportionately enlarged abdomen relative to gestational dates, dyspnea, dependent edema, ease of ballottement of the fetus and difficulty in mapping fetal position. The amount of fluid present was not recorded. The investigations of Augustin[2] indicate that the mean volume of amniotic fluid in hydramnios approximates 5 liters against a normal value of perhaps 600 cc. Taussig[3] reported 18 cases of hydramnios in which 3 to 5 liters of fluid were present and 6 cases with a volume of 5 or more liters.

The curve shown in Figure 1, constructed from Augustin's data, is recognized as the extreme segment of a distributional curve that when completed in terms of normal as well as abnormal pregnancies would enable computation of mean and extreme values for amniotic fluid on a statistical basis. The expectation is that a significant number of cases of hydramnios at the lower level (2 or 3 liters or less) of disease ordinarily pass unrecognized or at least unrecorded. For reasons to be considered later routine measurement of amniotic fluid at delivery might prove to have useful diagnostic and research applications. Analysis of blood, proteins and electrolyte content might also prove as informative as that of fluid removed from spinal or ventricular, pleural or pericardial cavities.

PREVALENCE AND INCIDENCE

Listed at the Boston Lying-in Hospital were 199 cases of hydramnios during the years 1923-1949, inclusive — a period during which 55,359 live births occurred. The rate of 3.59 per 1000 live births compares with that of Malpas,[4] who found a rate of 3.08 among 13,964 deliveries in Liverpool during the period 1923-1932; and the 3.0 per 1000 live births reported by Hiilesmaa[5] for 11,425 deliveries in Vipuri prior to 1945.

The case rate per 1000 live births per year at the Boston Lying-in Hospital is shown in Figure 2. No attempt is made to judge the significance of yearly fluctuations during the last twenty-five years as more and more infants were delivered in the hospital rather than the home. During each of the last three decades at the Boston Lying-in Hospital about 3.6 cases have been observed for each 1000 live births, a fact that suggests that hydramnios is a relatively stable phenomenon as regards long-term occurrence in Boston.

SEASONAL DISTRIBUTION

In this series, hydramnios is more prevalent (76:55) in women whose conceptions, as judged by recorded

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"last menstrual period," occur in the summer and fall. Figure 3 shows the distribution by month for 131 conceptions occurring between 1923 and 1950.

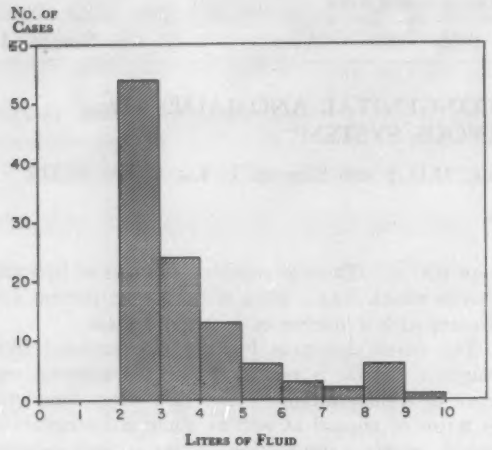

FIGURE 1. *Volume of Amniotic Fluid in 109 Cases of Hydramnios (According to Augustin,[5] 1928).*

A comparison group[6] of general deliveries at the Boston Lying-in Hospital between 1928 and 1950 shows a similar though less marked distribution (Fig. 4). Although 58 per cent of the conceptions leading to hydramnios occurred in the last half of the year, only 53 per cent of the general sample conceived at that time; there is no significant difference.

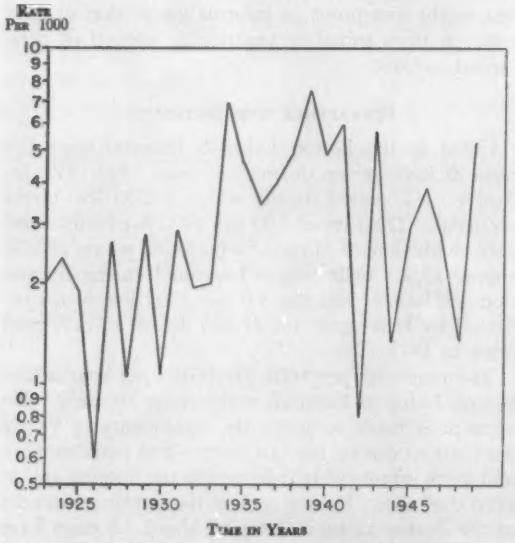

FIGURE 2. *Hydramnios — Case Rate by Year per 1000 Live Births, Boston Lying-in Hospital, 1925-1949.*

Mother's Age

Mothers with hydramnios were 2.65 years older than the mean of 25.74 years of age for mothers of the general population selected from Boston Lying-in Hospital records during 1928-52 inclusive[6] (Fig. 5). The difference in ages between primiparas in the hydramnios and comparison groups was not significant; however, multiparas were significantly older in the hydramnios group.

Birth Order

Comparison of the two groups cited above showed increasing birth order to be directly correlated with the appearance of hydramnios. Although maternal age and birth order are closely related, the data suggest that the factor of increasing birth order is more influential than maternal age.*

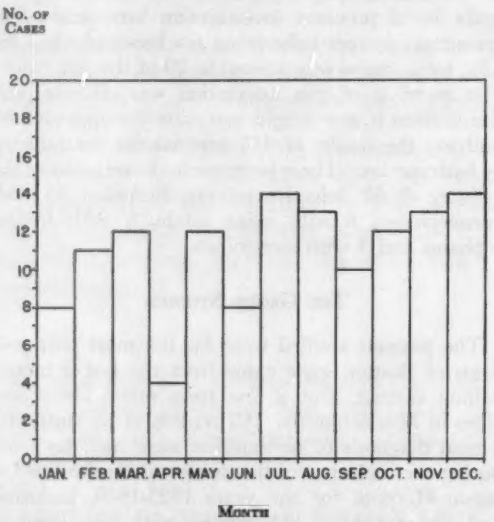

FIGURE 3. *Time of Last Menstrual Period by Month among 131 Mothers with Hydramnios, Boston Lying-in Hospital, 1935-1950.*

Parity

There were 303 other pregnancies occurring in mothers of this series, making a total of 448 conceptions among the 145 women with hydramnios; 16.5 per cent of these resulted in abnormal offspring (average frequency, 2.3 per cent at the Boston Lying-in Hospital[7]), 8.3 per cent in miscarriages, and 5.6 per cent in stillbirths. This rate of stillbirths is over two times that (2.5 per cent) found in the general population of Massachusetts for the five-year period 1939-1943,[8] inclusive, and that (2.7 per cent) found at the Boston Lying-in Hospital by Stevenson et al.[7]; it compares with the frequency (5.2 per cent) ob-

*For parity $X^2 = 26.9348$, $n = 4$, $p<0.001$; for age $X^2 = 13.6424$, $n=3$, $0.1>p>0.001$; for interaction of age and parity $X^2=21.607$, $n=3$, $p<0.001$.

served by Record and McKeown[9] for siblings of anencephalic babies in Great Britain. No comparison was available for miscarriage data. In all, 141 (31.5 per cent) of the 448 pregnancies of these mothers ended in death of the conceptus, as compared with less than 5 per cent for the general admissions.[7]

Mother's Health

Except for the occasional occurrence of respiratory infections, and 1 case of congenital syphilis, no instance of communicable disease was recorded in any of the histories.

Vaginal bleeding, characteristically in the first trimester of pregnancy, was observed in 27 (19 per cent) of the 145 pregnancies. This compares with the 13 per cent frequency of prenatal bleeding observed by Stevenson et al.[7] in their study of the experience at the Boston Lying-in Hospital.

Pre-eclampsia was diagnosed in 24 mothers in the last trimester of pregnancy. This represents a rate of 160 per 1000 hospital-delivered pregnancies as compared with a rate of around 50 for all mothers at the Boston Lying-in Hospital during the fifteen-year period 1916 through 1930.

Fifteen of 145 mothers were Rh negative when

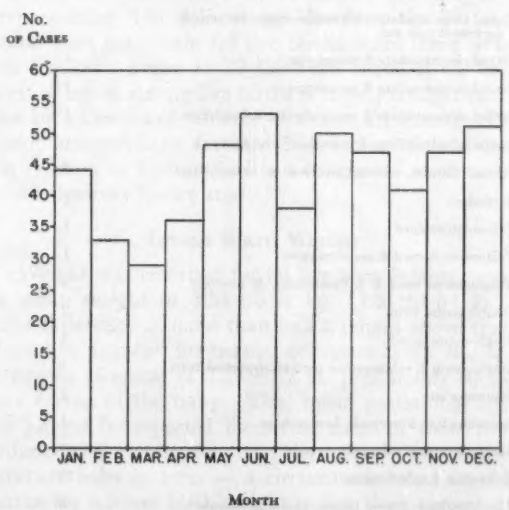

Figure 4. *Time of Last Menstrual Period by Month among 517 Mothers Selected at Random, Boston Lying-in Hospital, 1925-1950 (Data Compiled by the Departments of Epidemiology and Biostatistics, Harvard School of Public Health, from Records of the Boston Lying-in Hospital).*

their husbands were Rh positive. The frequency (10 per cent) is close to the 13 per cent expectancy for American marriages in which husband and wife are theoretically predisposed to the production of an infant with erythroblastosis.[10] However, 10 of the 145 deliveries resulted in erythroblastosis of the fetus, better than ten times the expectancy of 1 in over 200 deliveries. That one form of erythroblastosis is characterized by edema of the tissues and free fluid in the serous cavities of the fetus has long been recognized,[11] although an association with excess fluid in the amniotic cavity is not described in accounts of the condition that we have read.

Diabetes was present in 4 mothers during pregnancy and at the time of delivery. The number,

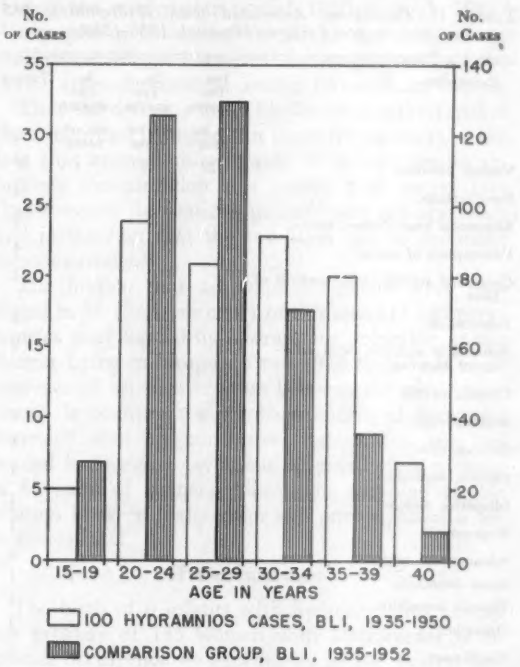

Figure 5. *Maternal Ages in Cases of Hydramnios and Comparison Group, Boston Lying-in Hospital.*

though small, is probably about ten times expectancy for the general population; hydramnios is a well recognized complication in diabetic pregnancies, being observed more commonly in patients with hyperglycemia than in those who are well controlled.

Other maternal conditions associated with hydramnios are listed in Table 1 according to frequencies with which they occurred. Four women underwent surgery during gestation; 1 mother underwent exploratory laparotomy eleven days after conclusion of her last menstrual period and ultimately gave birth to identical twins. One patient attempted abortion with ergot during early pregnancy that was marred only by hydramnios; a normal child was delivered at term. Another woman took quinine tablets, 0.12 gm. (2 gr.), two or three times daily during early pregnancy. Five (nearly 3 per cent) of the mothers were unmarried; the fact affords no basis for determining whether hydramnios is commonly associated with illegitimacy.

Placenta

The role of the placenta, cord and membranes in producing hydramnios has received occasional clinical comment but no systematic study. In this series 91 reports from the pathologist were available, of which only 24 described the placenta as normal. The most common diagnosis recorded was partial circumvallate placenta, identified at 27 (29 per cent) of the deliveries (Table 2); this is a highly significant occurrence and has received previous comment.[12]

Twenty-seven placentas showed infarction of a moderate to marked degree, often with old hemorrhage, calcification and necrosis, though the significance of this finding cannot be demonstrated. However, a relation of placental infarction to maternal hypertension has been shown by Zeek and Assali[13] in a study of placental tissues obtained from 232 women at the termination of pregnancy. Although placental infarcts were encountered in 83 per cent of the 71 patients with toxemia, they were found in only about 15 per cent of the 161 mothers without toxemia.

Five placentas had velamentous insertions of the umbilical cord. One of these came from a twin pregnancy in which the velamentous cord was associated with hydramnios and a papyraceous fetus; the other cord and amnion were normal and nourished a normal fetus. The circumstance is especially noteworthy because of the diagnosis of single-ovum pregnancy by the pathologist after inspection of placenta and membranes.

The placental weights for all live births recorded ranged from 250 to 1280 gm. (0.5 to 2.86 lb.), the mean weight being 696.5±249.3 gm. (1.54±0.55 lb.). According to Potter[14] the placenta usually weighs about one seventh of the infant's weight — according to Irving,[11] around one sixth. On this basis, the expected value based on infant weight for these cases would lie between 500 and 590 gm. and for the comparison group between 470 and 550 gm. The suggestion is that both infant and placenta are heavier than normal, a finding consistent with expected edema and the complications of diabetes and erythroblastosis.

Table 1. *Conditions Associated with Hydramnios, 145 Cases, Boston Lying-in Hospital, 1935-1950.*

Condition	1st Trimester No. of Cases	2d Trimester No. of Cases	3d Trimester No. of Cases	Totals
Vaginal bleeding	20	3	4	27
Pre-eclampsia				24
Rheumatic heart disease, severe				2
Fibromyoma of uterus				4
Congenital syphilis, with cirrhosis of liver				1
Tuberculosis				2
Automobile accident, with subsequent bleeding		2		2
Chronic pyelitis				1
Acute pyelitis	1		5	6
Ovarian cysts				1
Chronic nephritis				1
Idiopathic epilepsy				1
Hyperemesis	1			1
Adenomatous goiter				1
Acute bronchitis			1	1
Chronic bronchitis				1
Operation*	4			4
Illegitimacy				5
Severe anemia or hypoproteinemia or both				3
Diabetes				4

*Exploratory laparotomy, 11 days after last menstrual period — patient gave birth to twins; repair of anal fissure, 3d month; hemorrhoidectomy followed by vaginal bleeding, 2d month; decortication of sinuses followed by vaginal bleeding, 2d month.

Table 2. *Placental Types and Diseases.*

Type or Disease	No. of Cases
Negative mature	22
Negative immature	2
Massive infarction	1
Partial circumvallate	9
Partial circumvallate with erythroblastosis & infarction	2
Partial circumvallate with hemorrhage, necrosis & infarction	11
Partial circumvallate with hemorrhage, necrosis & persistent yolk sac	1
Partial circumvallate & marginata	1
Partial circumvallate & succenturiate	1
Partial circumvallate & succenturiate & battledore	1
Partial circumvallate & pseudo-erythroblastosis	1
Fibrin, fibrosis, edema, necrosis & hemorrhage	5
Battledore	1
Velamentous cord	1
Velamentous cord & membranacea	1
Velamentous cord & inflammation & necrosis	1
Double-ovum twin	2
Single-ovum twin	3
Single ovum & velamentous cord to abnormal twin	1
Succenturiate	2
Succenturiate & necrosis, hemorrhage	1
Succenturiate & velamentous cord	1
Infarction & calcification	10
Abnormalities of cord (knots, tumor & vascular anomaly)	8
Infarction & calcification in twin placenta	1
Erythroblastosis	5
Pseudo-erythroblastosis	1
Placenta praevia	1
Placenta accreta	2

Multiple Birth

The 146 pregnancies of the 145 women of this series were productive of 9 sets of twins (1:16 deliveries, compared with the expected 1:87) : 3 male, 2 female, 2 mixed and 2 of undisclosed sex. Two sets were described as double ovum, 3 as single ovum, 1 pair as di-chorionic and di-amniotic and both male, 1 as monochorionic and both male and 2 as not classified for sex or membranes. Of all twins only 4 infants were born alive. It is well established that approximately 10 to 15 per cent of pregnancies complicated by hydramnios terminate in delivery of twins,[2,3] and Augustin's series included 21 uniovular and 26 dizygotic sets. In the general population uniovular twins represent only 25 to 30 per cent of twin births. A twin pregnancy is apparently more likely than a simple pregnancy to accentuate critical mechanical, circulatory, metabolic and hematologic factors that may be acting together to produce hydramnios.

Sex of Infant

Seventy-two male and the same number of female infants were recorded; this undisturbed over-all sex ratio corresponds to the data of others. Details were lacking or inconclusive on 11 of the 155 progeny, representing 146 deliveries. However, the 1:1 sex ratio does not obtain for live births, since there were 49 live-born males to 29 live-born females; the excess of males among live births is largely compensated for by an excess of females — almost 4:1 among stillborn, anencephalic fetuses. The factor of fetal sex in relation to hydramnios and congenital malformations deserves future study.

Infant Birth Weight

Weight was recorded for 86 live-born infants, with a mean weight of 3.54 ± 0.54 kg. (7.81 ± 1.84 lb.). The difference of more than half a pound above that found by Ingalls[15] for normal deliveries at the Boston Lying-in Hospital of 7.25 ± 1.2 lb. presumably signifies edema of the baby. The mean gestational age as judged by reported menstrual dates of these live infants was nearly ten days less than that of the average baby at term — a circumstance that should make for a lesser birth weight rather than a greater.

Infant Death and Defect

Only 58 (37.4 per cent) living infants were born with no recognized congenital anomalies to the 145 women of this series. Fifty-nine fetuses, including defective ones, were stillborn; 5 were nonviable miscarriages, and 15 died in the neonatal period — a total intrauterine and neonatal mortality of 50.97 per cent. Sixty-eight of 155 progeny were born with recognized abnormalities; 49 of these were stillborn, and only 8 were discharged alive, the remainder dying during hospitalization. The striking association of hydramnios with anencephalus has been observed by other investigators. The relation to other deformities — spina bifida, hydrocephalus and mongolism — has not been enumerated or systematically explored.

Anencephalus

Anencephalus was the most common single gross defect discovered in 677 malformed infants among the 29,024 births at the Boston Lying-in Hospital during the twelve-year period 1930 through 1942.[7] Anencephalus accounted for 67 of the congenitally malformed infants born, and for more than half the major anomalies evident among 120 stillborn infants.

That the defect is in all likelihood acquired rather than inherited is implicit in these frequencies; in the fact that anencephalic infants do not survive to reproduce the condition as a genetic trait; in the fact that seasonal fluctuations in incidence are observed; and in the fact that the condition can be produced experimentally.[16]

The finding that anencephalic babies were produced in 34 (23.4 per cent) of this series of 145 pregnancies complicated by hydramnios occurring at the Boston Lying-in Hospital from 1920 to 1950 is clear evidence of an inter-relation between the two conditions. It confirms the corollary finding of Böök and Rayner[17] that "a conclusive hydramnion was recorded in 33 cases, i.e. about 50 percent" in a study of 67 cases of anencephalus. The meaning of this relation between hydramnios and anencephalus is yet to be clarified.

Hydrocephalus

The birth of 6 infants with hydrocephalus among the progeny of 145 women with hydramnios is no chance occurrence — expectancy at the Boston Lying-in Hospital being about 1 case for each 600 live births. Moreover, the association between hydrocephalus and anencephalus is already a matter of record as exemplified by Murphy's[18] studies indicating the familial tendency of the two conditions to accompany each other in successive pregnancies of the same mother.

Mongolism

Four cases of mongolism expectedly occur in about 2000 to 4000 births so that the observed frequency in this series is over twenty times the expectancy. The extensive evidence linking mongolism with disturbances of maternal health or uterine function has been summarized elsewhere.[19] Association with advanced maternal age was demonstrated many years ago and may be regarded as proved. Its significance remains problematical, but it is consistent with the idea that chronic as well as acute disturbances of maternal health play a part in the causation of mongolism.

Discussion

The essential clinical feature of hydramnios is an excess of fluid within the amniotic cavity. What is

known of factors governing accumulations of fluid in other body compartments, such as the peritoneal, pericardial and pleural cavities, suggests that the condition may be symptomatic of both local and generalized disturbances of circulatory dynamics. Ascites, pericardial effusion and pleurisy, all such dropsical conditions, are known to vary in degree depending on hydrostatic pressures and osmotic forces that include protein and electrolytic components. The essential epidemiologic feature of hydramnios, so far as it can be ascertained from this analysis, is the association with general metabolic and local placental disturbances that would be expected to embarrass placental-fetal circulation.

The high prevalence of erythroblastosis in this series focuses attention on the role of isoimmunization, fluid imbalance and perhaps anemia in hydramnios. The association between rhesus-factor incompatibilities and numerous breaks in the placental barrier and hemorrhage into the maternal intervillous spaces is well known, as is the fact that the golden-yellow, water-logged placenta is associated with edema and occasionally hydrops of the baby. That such fluid disturbances of the fetus involve anemia, hemorrhage, transudation, exudation, osmotic changes and stasis after immune reactions is well established. Less attention has been given to the role of erythroblastosis in the pathogenesis of hydramnios, although the implication is that sequences productive of hydrops in the baby produce hydrops in the amniotic cavity.

Toxemia, present over three times as often in mothers with hydramnios as in the general lying-in-hospital population, is further evidence of an association with a metabolic disturbance involving electrolyte and fluid imbalance. The eclamptic state, mild and severe, bears a demonstrable relation to infarctions of the placenta and to fetal death. Smith and Smith[20] report a fetal mortality of approximately 43 per cent in 94 toxic pregnancies studied by them. These pregnancies were associated with antecedent stillbirths, abortions and difficulties of a nature found in the mothers of the present group.

Similarly, diabetes is another metabolic disorder associated with toxemia and fluid imbalance; infarctions and edema of the placenta and excessive weight and high mortality of the fetus. Epidemiologic inter-relations among diabetes, toxemia and hydramnios are patent though the significance of the observation awaits interpretation.*

Apart from systemic factors controlling placental-fetal circulation there are local mechanical factors to be taken into account: abnormal insertion of the cord, described by others, notably Wilson,[22] who observed 5 eccentric, 9 marginal and 5 velamentous cords in 13 pairs of twins with hydramnios; knots and hematomas; infarcts strategically located near the insertion of the cord; and anomalies such as the short umbilical cords containing a single vein that characteristically nourish sireniform monsters (sympus dipus).

In the course of a consecutive study of placentas nourishing 20 deformed fetuses Talbot[23] found that placentas of anencephalic fetuses showed infarcts within a radius of 4 cm. from the base of the cord. Hydramnios complicated 4 of the 6 pregnancies productive of anencephalic babies; 1 was a twin pregnancy resulting in a living baby and an anencephalic stillborn fetus. The placenta of the living twin was normal except for a few small infarcts. That of the malformed baby was less than half the size of its twin and presented a V-shaped indentation at its circumference, the apex of which was almost contiguous with the base of the cord.

Although there are many structural and functional differences between the rodent and human placenta, it is interesting that massive hydrops within the placental membranes has been observed in mice after exposure of the pregnant female to high-altitude anoxia; 8 cases of this kind of hydramnios have been identified among 341 pregnant mice so treated in the laboratories of the Harvard School of Public Health. The resultant offspring have all been dead or defective at the time of cesarean section on the nineteenth day of gestation. Usually, they have been shrunken, dysplastic masses of fetal tissue corresponding to the macerated fetuses of human beings, but in 3 cases the fetus was recognizably well developed except for anencephaly — after anoxic insult on the eighth day of gestation. All but 2 cases have been present in animals rendered anoxic in the first half of pregnancy, and the condition was not observed among progeny of 155 control animals.

Conclusions

The indications are that hydramnios, anencephalus, fetal death and many "monstrosities" seen in association with them are interrelated components of maternal placental fetal disease.

Because of experimental observations and because the large majority of babies produced by women with hydramnios have defects of organs differentiating at an early stage of embryonic life, the assumption is made that hydramnios in the human being usually has its genesis in the first trimester of pregnancy.

The associated conditions, sometimes local, sometimes systemic, have a common action in their capacity to interfere with fetal and placental circulation, oxygen and fluid balance. The fact that hydramnios is frequently associated with anomalous development of both placenta and baby suggests that both defects are developing concomitantly and that they are manifestations of the same maternal disease. Laboratory evidence for this concept is fragmentary. Further study of the problem might profitably be

*Hoet and Osinski[21] have recently shown that the electrophoretic patterns of the amniotic fluid present in hydramnios in diabetic mothers is more like that of the mother than that of the infant. This implies that maternal protein enters into the cavity through some defect of the membranes and hydramnios is a consequence of the disturbed osmotic equilibrium.

pursued experimentally, with greater attention to the maternal organism as the environment of the fetus. Correlations should be sought among maternal history, physical examination, the course of pregnancy, the placental characteristics and the physical examination of the child.

The implication is that much placental disease with accompanying hydramnios and fetal death and defect is preventable with a better understanding of causation.

Enough has been learned to show that the challenge is not one of describing the pathogenesis of a specific clinical syndrome (hydramnios) but the exploration of a whole system of prenatal deaths and infant defects as manifestations of maternal disease. This is a complex undertaking involving the concerted exercise of many disciplines of both medicine and public health.

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OBSERVATIONS ON CANCER OF THE COLON AND RECTUM IN CONNECTICUT*

An Analysis Based on 5572 Proved Cases

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WILLIMANTIC AND NEW HAVEN, CONNECTICUT

THE Connecticut Tumor Registry has now been functioning for nineteen years. It is operated by the Division of Cancer and Other Chronic Diseases of the State Department of Health, in co-operation with the Connecticut State Medical Society, and 28 general hospitals, representing 93 per cent of all the general-hospital beds of the State. Observations based on a study of accumulated data reflect the work of several hundred surgeons in both small and large communities. Thus, an opportunity is afforded to obtain more accurate information about the general picture of cancer than is revealed by reports from single institutions.

During the past year, an exhaustive analysis was completed of all cases of cancer of the colon and rectum from 1935 to 1949. It is planned to publish detailed results of the study in the near future. The purpose of this paper, however, is to present certain highlights that may be of interest to the New England Surgical Society. All the statistical material was compiled in the Division of Cancer and Other Chronic Diseases of the Connecticut State Department of Health.

*Presented at the annual meeting of the New England Surgical Society, Bretton Woods, New Hampshire, October 9, 1954.

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Prevalence

Cancer of the colon and rectum is the most common cancer encountered in Connecticut (Table 1).

TABLE 1. *Comparative Frequency of Cancer of the Colon and Rectum and of Other Selected Sites.**

SITE	NO. OF CASES	PERCENTAGE
Colon & rectum	7699	16.4
Breast	6476	13.8
Cervix	2637	5.6
Lung	1840	3.9

*Total number of cancers of all types, 46,929.

From 1935 to 1949 there were 46,929 cases of cancer submitted to the Registry, and, of these, 7699 (16.4 per cent) occurred in the colon and rectum. Breast cancer was second in frequency, with 6476 cases, or 13.7 per cent of the total. Cancer of the cer-

vix and lung are shown only to demonstrate their comparative occurrence. There seems to be a growing impression that cancer of the lung is the most common of all cancers. In Connecticut it represents less

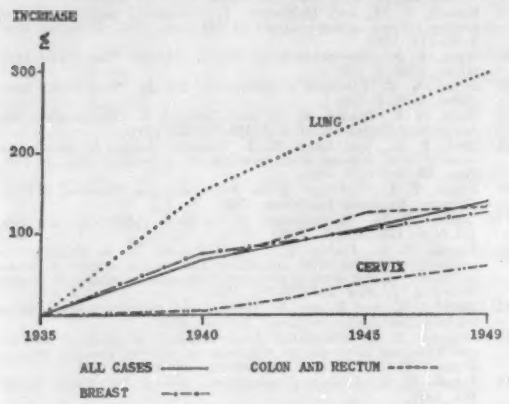

FIGURE 1. *Cases of Cancer in All Sites and in Selected Sites.*

than 4 per cent of all cases. It is true, however, that cancer of the lung from 1935 to 1949 increased about 300 per cent whereas the increase for cancer of all sites was approximately 140 per cent (Fig. 1). The increase in cancer of the colon and rectum was 137 per cent, or about the same as that for cancer in general. A discussion of the factors contributing to the remarkable increase in Connecticut since 1935 would be too lengthy for this presentation.

Of the 7699 cases of cancer of the colon and rectum 2127 were not proved microscopically, and are not included in this report, which is based only on the 5572 proved cases.

TABLE 2. *Distribution According to Site and Sex.*

SITE	MALE PATIENTS	FEMALE PATIENTS
Ascending colon	434(15.1%)	523(19.3%)
Transverse colon	161(5.6%)	223(8.2%)
Descending colon	825(28.8%)	927(34.2%)
Rectum & rectosigmoid	1434(50.1%)	1027(37.9%)
Unknown	11(0.4%)	7(0.3%)
Totals	2865	2707

SITE AND SEX

In this series the highest percentage of cases occurred in the rectum and rectosigmoid (Table 2). The lowest number was in the transverse colon. If the transverse colon is excepted, cancer of the bowel becomes steadily more frequent from the ascending colon to the rectum. This is the well recognized pattern commonly reported. Not so well recognized is the relation of sex to site distribution. Of the 5572 cases 2865 occurred in males, and 2707 in females, or an almost equal division. However, a study of Table 2 shows that, in all sites except the rectum and rectosigmoid, the disease was more common among females. For the rectum and rectosigmoid, the proportion among males was considerably higher than that among females — 50.1 per cent as compared to 37.9 per cent. The reason for this sharp reversal of prevalence is unknown.

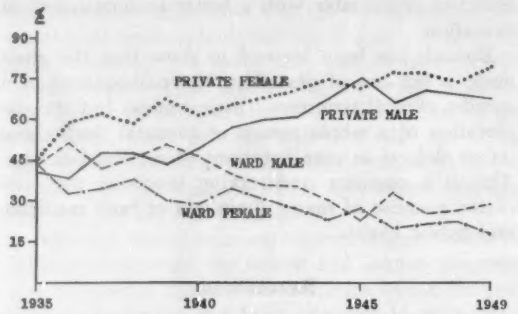

FIGURE 2. *Rates for Cancer of the Colon and Rectum, According to Hospital Status.*

STAGE OF DISEASE

All cases were classified as localized, occurring regionally (usually involving lymph nodes) or showing remote metastases. Of the 5572 cases 46.8 per cent were localized, and 30.8 per cent demonstrated regional involvement, whereas in 17.3 per cent remote metastases were apparent. The percentage of patients in the various stages of the disease was approximately the same for all sites from the ascending colon to the rectum (Table 3). It might have been reasonable to suspect that the disease would have been detected

TABLE 3. *Stage of Disease.*

SITE	TOTALS	LOCALIZED CASES	CASES WITH REGIONAL INVOLVEMENT	CASES WITH REMOTE METASTASES	CASES OF UNKNOWN STAGE
Ascending colon	957	425(44.4%)	328(34.2%)	174(18.2%)	30(3.1%)
Transverse colon	384	172(44.7%)	120(31.2%)	79(20.6%)	13(3.4%)
Descending colon	1752	830(47.3%)	522(29.8%)	316(18.0%)	84(4.8%)
Rectum & rectosigmoid	2461	1189(48.3%)	737(29.9%)	386(15.6%)	149(6.1%)
Unknown	18	3(16.7%)	5(27.7%)	7(38.9%)	3(16.7%)
Totals	5572	2619(46.8%)	1712(30.8%)	962(17.3%)	279(5.0%)

earlier in some sites than in others, but this did not prove to be true.

Furthermore, since all educational efforts have emphasized earlier suspicion of the disease by the patient and earlier recognition by the physician, it became of importance to determine whether or not more patients were being admitted in the early stages of the disease as the years went by.

From the first to the second five-year period the percentage of cases with localized disease on admission remained approximately the same (Table 4). There was a drop of 4.6 per cent in cases with remote metastases, and a corresponding rise of 7.2 per cent in those with regional involvement. From the second to the third five-year period, the rate of localized cases dropped over 10 per cent, with a compensatory rise in the proportion of cases with regional involvement. One may suspect that some of this change represents greater zeal on the part of pathologists in searching for lymph nodes in the operative specimen. However, in the last two five-year periods, the percentage of cases with remote metastases on admission has remained approximately the same. This is a discouraging group, and the task of diminishing its number is a challenge to both education and science.

TABLE 4. *Stage of Disease of Private and Ward Patients.*

PERIOD	LOCALIZED CASES	CASES WITH REGIONAL INVOLVEMENT	CASES WITH REMOTE METASTASES
1935 - 1939	556(50.1%)	257(23.2%)	231(20.8%)
1940 - 1944	838(49.6%)	513(30.4%)	273(16.2%)
1945 - 1949	1225(44.1%)	942(34.0%)	458(16.5%)
Total private patients	1752(48.0%)	1157(31.7%)	573(15.7%)
Total ward patients	764(45.2%)	496(29.3%)	357(21.1%)

TABLE 5. *Stage of Disease and Grade.*

GRADE	LOCALIZED CASES	CASES WITH REGIONAL INVOLVEMENT	CASES WITH REMOTE METASTASES	CASES OF UNKNOWN STAGE
1	258(66.5%)	73(18.8%)	29(7.5%)	28(7.2%)
2	1288(49.1%)	883(33.6%)	350(13.3%)	104(4.0%)
3	203(35.9%)	220(38.9%)	119(21.1%)	23(4.1%)
Not stated	870(43.6%)	536(26.9%)	464(23.3%)	124(6.2%)

It must be acknowledged that many factors contribute to the stage of the disease on admission. Table 4 presents comparative data for ward and private patients. For the entire group there was a greater proportion of localized cancer among private patients and a higher percentage of cases with remote metastases among ward patients. This was particularly true of cancer of the rectum and rectosigmoid, but not significantly so in other sites.

It is well known that the past few years have witnessed a rapid growth of insurance plans for patients with lower incomes. The number of private patients in this series rose in the fifteen-year period from 51.3 per cent to 72.3 per cent, whereas that of ward patients decreased from 41.8 per cent to 24.3 per cent (Fig. 2), with a negligible sex differential. Thus,

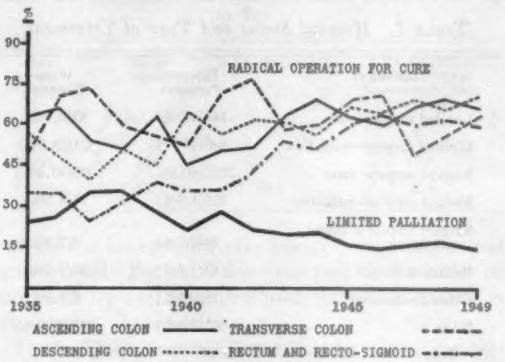

FIGURE 3. *Types of Operation Performed for Cancer of the Colon and Rectum.*

many patients who formerly would have been in the ward are now being admitted to private services. It would be phenomenal if intelligence, and greater awareness of early symptoms, kept pace with the increase of insurance plans.

Another strong influence on the stage of disease is the grade of the tumor. There is a striking tendency for highly differentiated tumors to remain localized, in this series over 66 per cent, whereas only 7.5 per cent of patients had remote metastases on admission (Table 5). Conversely, of the Grade 3 tumors, only 35.9 per cent were localized, and more than 21 per cent were associated with remote metastases. This held true for all sites in the large bowel, but particularly in the rectum and rectosigmoid, where over 70 per cent of the Grade 1 tumors were localized on admission.

TABLE 6. *"Curative" Surgery in Localized Cases, According to Site.*

SITE	PATIENTS HAVING "CURATIVE" SURGERY
	%
Ascending colon	85.9
Transverse colon	84.9
Descending colon	79.8
Rectum & rectosigmoid	76.4

TREATMENT

As was expected, the study showed that radical operations for cure were being performed in a significantly higher percentage of patients in 1949 than in 1935. Of the entire series of 5572 patients 56.1 per cent had radical surgery for cure, but the figure rose from 47.8 per cent in 1935 to 63.9 per cent in 1949 (Fig. 3). For the fifteen-year period, the rise in radical operations for cure was least spectacular in the

ascending colon, because here the rate had always been relatively high (over 60 per cent). It was most apparent in the rectum and rectosigmoid, where the frequency of radical operations rose from 35 per cent in 1935 to a high of over 62 per cent in 1946. As the proportion of radical operations increased, there was a corresponding decrease in palliative procedures.

TABLE 7. *Hospital Status and Type of Treatment.*

TREATMENT	PRIVATE PATIENTS	WARD PATIENTS
Limited surgery—cure	147(4.0%)	45(2.7%)
Limited surgery—palliation	646(17.7%)	421(24.9%)
Radical surgery—cure	2222(60.9%)	803(47.4%)
Radical surgery—palliation	253(6.9%)	77(4.5%)
Surgery (intent & extent unknown)	24(0.7%)	5(0.3%)
Radiation alone	40(1.1%)	15(0.9%)
Other (unknown)	10(0.3%)	5(0.3%)
None	307(8.4%)	321(19.0%)
Totals	3649	1692

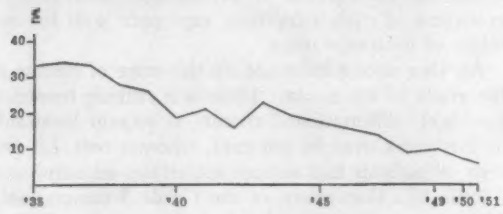

FIGURE 4. *Operative Mortality among 3470 Radical Operations.*

"Curative" surgery was undertaken most often in the cases in which the disease was considered to be localized (Table 6). The term "curative" surgery is used here advisedly and includes not only radical surgery but also, in a small group of cases, limited surgical procedures performed for localized lesions, many of them polyps, which proved to be malignant on microscopical examination. This group is referred to again under the discussion of results.

TABLE 8. *Mortality in Radical Operations According to Sex.*

SITE OF LESION	DEATHS AMONG MALE PATIENTS	DEATHS AMONG FEMALE PATIENTS
Ascending colon	291(18.2%)	362(20.4%)
Transverse colon	105(19.0%)	167(17.4%)
Descending colon	556(20.1%)	642(12.3%)
Rectum & rectosigmoid	749(21.0%)	596(13.9%)
Totals*	1701(20.2%)	1767(15.0%)

*For colon and rectum.

A far greater proportion of private patients underwent radical surgery for cure than ward patients, 60.9 per cent as compared to 47.4 per cent (Table 7). This applied to both males and females. Among ward patients 19 per cent and only 8.4 per cent of private patients received no treatment.

OPERATIVE MORTALITY

In the fifteen-year period there were 3470 radical operations, with 608 deaths, or an operative mortality of 17.5 per cent (Fig. 4). This figure dropped from 33 per cent in 1935 to 9.4 per cent in 1948; in 1951 it was only 6 per cent. The decrease applied almost equally to all sites in the large bowel, and there was no statistically significant difference between private and ward patients.

TABLE 9. *Mortality of Radical Operations According to Size of Hospital.*

NO. OF RADICAL OPERATIONS	MORTALITY
	%
Under 100	21.2
100 - 300	18.6
More than 300	15.7

There was, however, an appreciably higher mortality among males than females. The total number of radical operations was almost equally divided, and yet operative mortality for males was 20.2 per cent and that for females 15 per cent (Table 8). With the exception of the ascending colon, in which the operative mortality was slightly higher for females, operation from the transverse colon to the rectum became increasingly less favorable for males.

TABLE 10. *Five-Year End Results According to Year.*

YEAR	5-YR. SURVIVAL	5-YR. SURVIVAL WITH PATIENT APPARENTLY FREE FROM CANCER
	%	%
1935	14.3	13.2
1936	17.9	15.8
1937	10.8	10.4
1938	17.8	16.1
1939	22.4	20.3
1940	22.7	21.6
1941	24.7	22.1
1942	25.6	23.2
1943	24.9	23.1
1944	22.2	20.0
1935 - 1944 (2797 cases)	21.3	19.4

Operative mortality was lowest when radical operations were performed in the localized stage of the disease. If there was regional involvement, or when radical surgery was attempted in the presence of remote metastases, the rate increased rapidly.

In addition, there was a wide variation in mortality among the reporting hospitals, ranging from 0 to 50

per cent. In some of the smaller hospitals, the number of radical operations was too small to have statistical validity. In general, as the number of radical operations increased in a given hospital, the operative mortality became lower (Table 9).

Results

Five-year results were available for the years 1935 through 1944. Only 1.6 per cent of patients were lost to follow-up study during the first five years after diagnosis. End results were calculated according to the method recommended by the Joint Committee on Reporting Cancer End Results of the American College of Surgeons.

In the ten-year period there were 2797 patients, of whom 21.3 per cent survived for five years or more and 19.4 per cent were living and apparently free from cancer for a similar period (Table 10). Even though this is a low over-all salvage, from 1935 to 1944 the survival rate increased over 55 per cent, and the cure rate over 51 per cent (Table 10). No site in the large bowel was exempt from improvement, but both survival and cure rates became less favorable from the ascending colon to the rectum (Table 11). In the first five-year period the highest cure rate (21.7 per cent) was obtained for the ascending colon. In the second five-year period the highest was for the transverse colon (27 per cent). In both five-year periods the lowest cure rate was for the rectum and rectosigmoid. For each five-year period, the order of cure rates by site, arranged from highest to lowest, is presented in Table 12.

The survival and cure rates for females were significantly higher than those for males (Table 13). From 1935 to 1944, there were 1468 males and 1329 females with cancer of the colon and rectum. Of the males, 18.1 per cent survived for five years or more, as compared with 24.8 per cent of females, whereas 16.8 per cent of males gave no evidence of disease after five years, in contrast to 22.3 per cent of females.

Similarly, the factor of age seemed to have an influence on five-year results (Table 14). There was a general decrease in five-year survival rates with increasing age, and this was true for both males and females. It was true also when the rates in each age group were adjusted for life expectancy, except that here the age-adjusted survival rates begin rising again at the age of seventy and reach the highest peak in the age group of seventy-five and over.

Table 11. *Five-Year End Results According to Site.*

Site	5-Yr. Survival	5-Yr. Survival with Patient Apparently Free from Cancer
	%	%
Ascending colon:		
1935 - 1939	22.8	21.7
1940 - 1944	26.1	24.6
Transverse colon:		
1935 - 1939	17.6	14.9
1940 - 1944	29.4	27.0
Descending colon:		
1935 - 1939	16.9	16.3
1940 - 1944	25.0	23.2
Rectum & rectosigmoid:		
1935 - 1939	15.3	13.1
1940 - 1944	22.0	19.5

Table 12. *Cure Rates According to Site from Highest to Lowest.*

Site	Cure Rate
	%
1935 - 1939:	
Ascending colon	22.8
Descending colon	17.6
Transverse colon	16.9
Rectum & rectosigmoid	15.3
1940 - 1944:	
Transverse colon	27.0
Ascending colon	24.6
Descending colon	23.2
Rectum & rectosigmoid	19.5

Table 13. *Five-Year Survival and Cure Rates According to Sex.*

Sex	No. of Patients	5-Yr. Survival	5-Yr. Survival with Patient Apparently Free from Cancer
		%	%
Males	1468	18.1	16.8
Females	1329	24.8	22.3

Table 14. *Five-Year Survival Rates According to Age and Sex (with Adjustment for Life Expectancy).*

Age	Patients Living after 5 Yr., or More	Life Expectancy for 5 Yr.*	5-Yr. Survival (Adjusted for Life Expectancy)
yr.	%	%	%
Males:			
Under 45	28.5	97.2	29.3
45-49	28.1	94.8	29.6
50-54	21.1	92.2	22.9
55-59	20.8	88.7	23.4
60-64	18.1	83.9	21.6
65-69	11.5	77.1	14.9
70-74	11.3	67.0	16.9
75 & over	10.7	45.4	23.6
Females:			
Under 45	34.5	98.3	35.1
45-49	24.1	96.5	25.0
50-54	26.8	94.9	28.2
55-59	25.7	92.3	27.8
60-64	25.1	88.4	28.4
65-69	18.8	82.0	22.9
70-74	19.4	72.2	26.9
75 & over	18.2	50.2	36.3

*Figures computed from United States life tables for 1939 - 1941. Percentage represents proportion of people in general population of corresponding age expected to survive for 5 years. Life tables computed on assumption that mortality conditions existing in 1939 - 1941 would continue. Division of observed 5-year survival rate for patients with cancer of colon and rectum by corresponding life-expectancy rate gives survival rate adjusted for life expectancy; rates can then be compared among age groups.

The economic status of the patient also seemed to have some effect on end results. Both survival and cure rates were definitely higher among private than among ward patients (Table 15). This applied to the entire group as well as to both male and female patients. The difference in survival and cure rates between male and female ward patients was not statistically significant. The best end results of all were obtained among female private patients.

TABLE 15. *Five-Year Survivals According to Hospital Status and Sex.*

STATUS	NO. OF PATIENTS	5-YR. SURVIVAL	5-YR. SURVIVAL WITH PATIENT APPARENTLY FREE FROM CANCER
		%	%
Male patients:			
Private	780	20.6	19.1
Ward	608	15.1	14.3
Female patients:			
Private	864	27.4	24.5
Ward	410	19.8	17.8

So far as the influence of the stage of the disease on end results is concerned, one would not, of course, expect any improvement in survival rates among those who had remote metastases on admission. The five-year survival and cure rates for patients with cancer with involvement of regional lymph nodes were only slightly better in the second five-year period than in the first (Table 16). Survival and cure rates, however, were considerably higher for those whose disease was localized on admission.

TABLE 16. *Five-Year Survival According to Stage of Disease.*

PERIOD	PATIENTS IN GROUP	5-YR. SURVIVAL	5-YR. SURVIVAL WITH PATIENT APPARENTLY FREE FROM CANCER
	%	%	%
Localized cases:			
1935 - 1939	50.1	25.2	23.4
1940 - 1944	49.6	35.0	32.7
Regional-lymph-node involvement:			
1935 - 1939	23.2	15.6	14.4
1940 - 1944	30.4	18.7	16.6
Remote metastases:			
1935 - 1939	20.8	0.4	0.0
1940 - 1944	16.2	0.7	0.4

The grade of the tumor apparently had a decisive effect on the end results, although the number of tumors graded suggests that conclusions be drawn cautiously. In the transverse colon, the number of Grade 1 tumors was too small to be statistically trustworthy, but in all other sites the difference in both survival and cure rates between Grade 1 and Grade 3 tumors was noteworthy. In the rectum and rectosigmoid, for example, the survival rate was 36.3 per cent for Grade 1 tumors and only 8.5 per cent for Grade 3 tumors (Table 17).

The most common types of treatment rendered in this series are shown in Table 18. Of the 1373 patients who had radical surgery for cure 36.9 per cent survived for five years or more. Only 2.1 per cent of patients who had radical surgery for palliation survived for five years. Of those who had limited surgery for cure, 40.1 per cent survived for five years.

A careful review of the 142 cases in the last group revealed that many of them were malignant polyps. Since this group may well represent cancer of the bowel in its earliest stage and since nearly 60 per cent of the patients failed to survive for five years after removal by localized procedures, the justification for conservative surgery in this type of case might be seriously questioned.

TABLE 17. *Five-Year Survival by Grade and Site of Lesion.*

GRADE	5-YR. SURVIVAL	5-YR. SURVIVAL WITH PATIENT APPARENTLY FREE FROM CANCER
	%	%
Ascending colon:		
1	40.0	40.0
2	35.2	34.6
3	18.2	16.4
Transverse colon:		
1	18.2	18.2
2	33.0	29.7
3	15.4	15.4
Descending colon:		
1	32.9	32.9
2	27.7	25.1
3	18.8	18.8
Rectum & rectosigmoid:		
1	36.3	32.7
2	21.1	19.0
3	8.5	8.5

The most favorable results, of course, were noted in patients who survived radical operation for cure (Table 19). There were 1072 patients in this group, and 47.2 per cent survived for five years or more. The best results were obtained in the ascending colon, with a 53.6 per cent survival rate, and the poorest results in the rectum and rectosigmoid, with a rate of 42.5 per cent. The five-year survival rates for the transverse colon and descending colon were 47.5 per cent and 48.9 per cent respectively. It must be emphasized that these results apply only to a highly se-

TABLE 18. *Five-Year Survival after Surgery.*

TYPE OF OPERATION	NO. OF CASES	5-YR. SURVIVAL	5-YR. SURVIVAL WITH PATIENT APPARENTLY FREE FROM CANCER
		%	%
Limited surgery for cure	142	40.1	38.0
Limited surgery for palliation	689	1.7	0.1
Radical surgery for cure	1373	36.9	34.8
Radical surgery for palliation	141	2.1	0.7

lective group and present the picture of cancer of the colon and rectum in its most favorable aspect. By too much emphasis on patients who survived radical operation for cure, one can be left with an unrealistically optimistic concept of the total problem.

TABLE 19. *Five-Year Survival and Cure Rates after Survival of Radical Surgery.*

SITE	NO. OF CASES	5-YR. SURVIVAL	5-YR. SURVIVAL WITH PATIENT APPARENTLY FREE FROM CANCER
		%	%
Ascending colon	194	53.6	51.0
Transverse colon	99	47.5	44.4
Descending colon	370	48.9	46.5
Rectum & rectosigmoid	409	42.5	39.9
Total	1072		
Averages		47.2	44.6

CONCLUSIONS

Much of what has been said above might be epitomized by the postulation that the ideal patient with cancer of the large bowel is a woman, seventy-five years of age, who is a private patient, who has a localized lesion in the ascending colon of Grade 1 malignancy, and who has survived the radical operation for cure.

One of the advantages of a tumor registry such as that in Connecticut is that the statistical data that emerge offer a basis for a dispassionate analytical appraisal of accomplishments and failures down through the years. As a result of this study, it might be said that progress in the management of cancer of the colon and rectum is slow but real. Whatever the magnitude of improvement, it can scarcely be attributed to the fact that patients are now being admitted in an earlier stage of the disease than they were ten years ago. Here, it appears that education has been ineffective. Rather, progress seems to have followed largely from the ability of more and more surgeons to perform radical operations with a steadily decreasing mortality. Although further progress may be anticipated along this line, any material change for the better in end results must await a plan for detecting more cases of cancer of the large bowel in its localized stage. This may not occur until the biologic characteristics of cancer in general, and of the colon and rectum in particular, are better understood.

We are indebted to Dr. Matthew Griswold, chief of the Division of Cancer and Other Chronic Diseases of the Connecticut State Department of Health, and particularly to Mr. Earl Pollack, research statistician, and Mr. Charles Wilder, research associate, and the entire staff of the Division, whose painstaking work made this study possible.

A great amount of supplementary information is available in the form of statistical tables and charts, which the authors will be glad to send to those interested.

SUCCESSFUL SUTURE OF RUPTURED MYOCARDIUM AFTER NONPENETRATING INJURY*

GERARD DESFORGES, M.D.,† WILLIAM P. RIDDER, M.D.,‡ AND RALPH J. LENOCI, M.D.§

BOSTON AND QUINCY, MASSACHUSETTS

PENETRATING injuries of the heart secondary to bullet or stab wounds are not uncommon. Their diagnosis is not difficult, and management of such cases by conservative and surgical measures has surprisingly good results.[1-4] Not so well appreciated, however, is another type of cardiac trauma produced by concussive or contusive forces. Such injuries may also lead to disruption of cardiac musculature, serious hemorrhage and an ultimately fatal issue if not discovered and treated promptly.[5,6] Bright and Beck,[5] in an extensive review of 168 fatal cases, revealed that, of these, 30 patients who lived longer than an hour might have been helped by surgery.

Recently, we successfully treated what, as far as we can determine, appears to be the first case of cardiac rupture secondary to nonpenetrating trauma so handled. This case is as follows:

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CASE REPORT

T. C. (Q.C.H. 241614) was brought by ambulance to the emergency room at 2:35 a.m. on September 7, 1954, immediately after an automobile accident. He stated that he was lying asleep in the rear seat of an automobile, said to have been traveling at a high rate of speed, when it struck a large tree head-on. The driver of the car was killed instantly, and the patient was believed to have been thrown against the front seat.

On admission he was stuporous but could be aroused. He was bleeding from the nose and mouth. The initial blood pressure was 70/20, the pulse 80, and the respirations 30 and shallow. Blood typing and crossmatching were begun immediately, and intravenous administration of dextran was started. Tracheal suction, oxygen by nasal catheter and general supportive treatment were instituted.

Physical examination revealed rapid, shallow breathing, with an intact rib cage. There was cyanosis of the nailbeds, lips and ears. Dullness on percussion, with diminished breath sounds, was noted over the right chest. The trachea was shifted to the left. The left side of the chest was clear, and the heart sounds were regular and of good quality.

Abdominal examination revealed a tense, tender upper abdomen, with muscle rigidity in both upper quadrants. The lower abdomen was soft and nontender. Bowel sounds were diminished. There were no palpable masses or shifting dullness. The bladder was catheterized, and clear urine was obtained.

There was obvious deformity of the left thigh in the middle third, with massive swelling, suggesting a fracture of the

femoral shaft. A fracture of the nose, with slight displacement to the right, was noted.

X-ray examinations of the chest, abdomen and left thigh were made with a portable machine while supportive treatment was in progress. A film of the chest showed a diffuse haze over the right lung. The mediastinum was shifted to the left. No rib fracture was evident. A comminuted fracture of the midportion of the left femur was demonstrated

FIGURE 1. *Film of the Chest Taken with a Portable Machine Seven Hours after Admission, Showing Extensive Hemothorax and Marked Mediastinal Shift.*

on a film of the extremity. Films of the abdomen with the patient flat and in the right lateral decubitus position disclosed no abnormality.

A hematocrit of 34 per cent was obtained on the initial blood sample. While whole blood was being administered thoracentesis was performed, and 675 cc. of bright-red blood was removed from the right pleural cavity. The patient immediately improved, cyanosis diminished, the respirations fell to 24, and the blood pressure rose concomitantly with continued transfusion to 104/80. The pulse was 100 and was of good quality. A check film of the chest taken with a portable machine showed minimal haziness over the right lung. The mediastinum was in normal position. Approximately 2½ hours after admission, the hematocrit had risen to 41 per cent, and the situation seemed stabilized. A Steinmann pin was inserted through the left tibial tubercle under local anesthesia, and the left leg was placed in balanced suspension.

Five hours after admission the patient was transferred to a surgical ward. During the next 2 hours his condition gradually worsened. The blood pressure rose to 150/50, the pulse to 120, and the respirations to 40. Whole blood was continued, and a repeat film of the chest was obtained. Examination of the chest revealed return of dullness on the right, tracheal shift to the left and diminution of breath sounds over the right lung. While the chest film (Fig. 1) was being developed he suddenly coughed and simultaneously vomited some old blood. He became comatose, extremely cyanotic and pulseless. Immediate thoracentesis was done, with removal of 2000 cc. of fresh bright-red blood from the right pleural cavity. His condition again improved. The pulse steadied at 120, and the blood pressure rose to 160/60. Respirations fell somewhat to 36 but remained shallow.

Nine hours after admission, with 2 blood transfusions being administered simultaneously, thoracotomy on the right was done under endotracheal anesthesia.

When the right side of the chest was opened several hundred cubic centimeters of fresh blood was found. There was a large hematoma in the right middle lobe anteriorly. With the lung collapsed exploration was continued, and as the lung was retracted from the mediastinum blood gushed into the thorax from a longitudinal rent in the pericardium overlying the right atrium. A 4-cm. longitudinal tear in the right atrium and superior vena cava at their junction (Fig. 2) was identified and occluded with 2 large triangular lung clamps. A simple running suture of No. 000 black silk was used to close the tear in the atrium and vena cava. The pericardial rent was left open, and the chest closed after a catheter had been placed for underwater drainage. At the conclusion of the procedure the patient was in good condition, with a blood pressure of 110/60, a pulse of 90 and respirations of 40. Four units of whole blood was administered during the 1½-hour procedure, and 2 units was given postoperatively.

Convalescence was uneventful. The temperature and pulse had returned to normal levels by the 5th postoperative day. Electrocardiograms remained normal. On the 9th day an intramedullary nailing of the left femur was performed. On the 21st day after injury he was transferred to a Veterans Administration facility at his request for further convalescence and possible nasal surgery.

Two months after the cardiac surgery he was up and about on crutches, with no symptoms referable to the cardiovascular system.

DISCUSSION

Although one is accustomed to consider the brain, liver, kidneys and spleen as susceptible to compressive and contusive injury, the possibility of such an injury to the heart is frequently overlooked. Sigler[7] has shown that, of 42 cases with extensive trauma to the body after serious accidental injuries, in 32, or 76.2 per cent, there was clinical or electrocardiographic

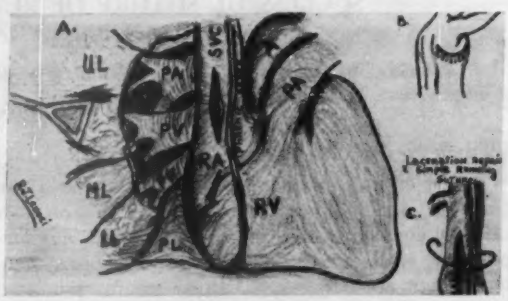

FIGURE 2. *Diagrammatic Representation of the Longitudinal Laceration of the Superior Vena Cava and Right Atrium* (A), *with the Thoracotomy Site* (B) *and Repair of the Laceration* (C) *with a Simple Running Suture of Fine Silk.*

evidence of cardiac damage that would not have been suspected unless carefully sought.

On the basis of their analysis Bright and Beck[5] have outlined as follows the various ways in which nonpenetrating wounds of the heart are produced:

1. Bursting of the heart by compressing it between the sternum and vertebrae much as a toy balloon can be compressed in one's hand.
2. Contusion of the heart with subsequent softening of the area of contusion.
3. Increased intracardiac pressure. This may be brought about by the application of forces directly to the heart, or it may be produced by the application of indirect forces as by sudden compression of the legs and abdomen.

Undoubtedly, rupture of an intact, healthy myocardium after trauma to the body can conceivably occur only as a result of profound changes in the intrathoracic and intracardiac pressure.

In experimental attempts, Bright and Beck[5] noted that the pressure in the right atrium could be greatly elevated in dogs by compression of the legs and abdomen. Even though they were not successful in causing atrial rupture they succeeded in producing petechiae under the endocardium. We believe that it is perhaps the speed in which the atrial pressure changes take place that leads to rupture. Impact violence such as that in the case reported above leads to instantaneous pressure change and hence the most devastating type of disruptive force on an elastic body. Crane[6] reports 3 fatal cases of cardiac rupture secondary to nonpenetrating trauma, 2 of which were in automobile mishaps similar to that in the case reported above.

Surprisingly, all chambers of the heart are equally vulnerable to rupture. Again, in the review of Bright and Beck,[5] the right atrium was ruptured in 36 cases, the left atrium in 30, the right ventricle in 31, and the left ventricle in 37. More than one chamber was ruptured in 13, and the interventricular septum was opened in 13 cases. The interatrial septum was lacerated in only 1 case.

In 76 cases of cardiac rupture in their series[5] death was due neither to the cardiac rupture per se nor to exsanguination. At the time of the autopsy, cardiac tamponade was the only finding noted that was sufficiently important to have caused death. In 23 cases there was extensive hemothorax. The remaining patients died of multiple extensive injuries or complications such as pneumonia and pericarditis.

How can the diagnosis of cardiac rupture after nonpenetrating injury be made? We believe that clinically this may be difficult or impossible. Perhaps, the best one can do is have an intelligent suspicion when dealing with extensive injuries capable of producing chest compression or rapid increase in intravascular venous pressures such as abdominal compression. If the pericardium remains intact the patient will present the picture of tamponade, and if this cannot be handled successfully by several pericardiocenteses, we consider it safer to carry out surgical exploration. The associated laceration of the pericardium, as in the case reported above, obviously leads to massive hemothorax and signs of marked blood loss. Likewise, if several thoracenteses are not successful, exploration is advisable, with rupture of the heart as a possibility that may have to be dealt with kept in mind.

We believe that it is important not to delay surgery too long. The common concept that most intrathoracic hemorrhage either is immediately fatal or will soon stop spontaneously is fraught with danger and may cost the patient his life.

Summary

A case of cardiac rupture after nonpenetrating chest trauma, with successful operative repair, is reported. This is believed to be the first such case so treated.

The importance of suspicion of possible great-vessel or cardiac damage secondary to nonpenetrating injuries is emphasized.

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SPECIAL ARTICLE

CHANGING PATTERNS OF RESISTANCE OF CERTAIN COMMON PATHOGENIC BACTERIA TO ANTIMICROBIAL AGENTS*

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BOSTON

DURING the past few years workers at the Thorndike Memorial Laboratory have collected a considerable number of data on the in vitro susceptibility of common pathogenic bacteria to the various antibiotics that have been generally available. On occasions when new antibiotics were under clinical trial, consecutive strains of different species obtained either in pure culture or as the predominant organisms in mixed cultures from clinical material were tested for susceptibility to those agents to define their antibacterial effect on organisms encountered in the hospital at that time. On other occasions special studies were carried out in which successive strains of individual species or of closely related organisms were collected as they became available from current clinical materials, and these were tested simultaneously for their susceptibility to all the antibiotics available at that time. The minimum inhibiting concentration of each antibiotic required for the different strains of the same species were then depicted graphically in a single cumulative distribution curve. Such curves constructed for all the antibiotics, when shown together, constituted what was called the antibiotic spectrum for that particular bacterial species.

ANTIBIOTIC SPECTRUM

Such antibiotic spectrums may be of practical value since they are based on tests carried out in nearly the same fashion, modified only by changes in the medium made necessary by the specific growth requirements of certain species, and are all expressed in the same unit — namely, micrograms of antibiotic per cubic centimeter of medium. Several important relations are apparent from even superficial observations of some of these spectrums. Each curve constituting the spectrum of any given species shows at a glance the extent of the variation in the susceptibility of different strains of that species to any given antibiotic. The group of curves making up that spectrum also depicts the relative activity of different antibiotics against all the strains of that species that were tested and generally permits an alignment of the different antibiotics in the order of their in vitro activity. It is also possible to compare the activity of the same antibiotics on different or related species by comparing the antibiotic spectrums of these species. Finally, what is most pertinent for the subject of this paper, such data collected at different times offer an opportunity to observe changes in the susceptibility of strains of various species to the different antibiotics, and thus perhaps reflect the effects of the extensive use of any given antimicrobial agents and the susceptibility of different bacteria to the same and to different agents.

The significance of these relations must, of course, also take into account many factors entering into the cultivation of the organisms as they affect the results obtained by the methods used in the in vitro tests. The wide limits of error involved in the twofold dilution method employed throughout these studies must also be taken into account in any comparisons. The results and comparisons are therefore valid only under the conditions and within the wide limits of error of these tests. Their interpretations in terms of relative therapeutic effectiveness may depend, on the one hand, on many additional factors relating to the reaction of the host to the different pathogenic organisms and, on the other hand, on the properties of the antibiotics that relate to their interaction with the infecting organisms within the host.

Examples of antibiotic spectrums of certain species of bacteria as derived from material collected at the Boston City Hospital and published some time ago will serve to illustrate some of these features.‡ The antibiotic spectrum of the pneumococcus,[1] based on strains collected and tested in 1949 and earlier, shows the clean separation of the individual curves representing the cumulative distribution of the minimum inhibiting concentrations of all the strains that were tested with each of the 7 antibiotics that were studied. This permits a ready listing of these 7 agents in the order of their in vitro inhibitory activity on a weight basis by notation of the antibiotics represented by these curves from the most active on the left to the least active on the right. From this figure the order of activity is as follows: penicillin, chlortetracycline, chloramphenicol, bacitracin, streptomycin, polymyxin B and polymyxin D.§ Moreover, the shape of the in-

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Presented at the Second Annual Symposium on Antibiotics, Washington, D.C., October 25, 1954, by invitation of the Chairman. Reprinted, with some changes, from *Antibiotics Annual 1954-55* with the permission of the editor-in-chief, Henry Welch, Ph.D.

The studies on which this paper is based were carried out with many collaborators and are reported in detail in several publications referred to in the text. The work was aided by a grant from the United States Public Health Service.

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‡The text-figures representing the antibiotic spectrums to which references are being made are not reproduced here; they are to be found in the original articles cited.

§The trade-mark for chlortetracycline is Aureomycin, that for chloramphenicol is Chloromycetin, and that for polymyxin D is Aerosporin.

dividual curves, their steep slope throughout almost their entire length and the relatively short lower and upper portions of their "S" shape reflect the striking uniformity of the minimum inhibiting concentrations of the different strains to the same antibiotic in every instance.

The clear, quantitative differentiation of the activity of the various antibiotics against pneumococcus is in striking contrast to the situation found during the same period when strains of *Haemophilus influenzae* were tested with the same antibiotics.[2] Against these organisms 6 of the 7 antibiotics had quantitatively similar inhibiting action; only bacitracin appeared to be practically ineffective, and the curve representing this antibiotic stands apart from the others. However, the slope of the streptomycin curve appears to be somewhat less steep than that representing the other active antibiotics, indicating the wider range of concentrations required to inhibit different strains of this species. Strains of *H. influenzae* of great resistance even to this antibiotic were not encountered during the study, which included only strains isolated and tested in 1949 and earlier.

A similar investigation carried out with streptococci[3] illustrates the differences in activity of the same antibiotics against different generic (as opposed to serologic) groups of streptococci. In the graphic representation of the activity of the different antibiotics against beta hemolytic streptococci of Group A, the shape of the individual curves and the alignment of the curves representing the different antibiotics appeared grossly similar to those previously noted with pneumococci. There were some quantitative differences, however, in the activity of individual agents against pneumococci as compared with the Group A streptococci. Moreover, the position of the bacitracin curve was altered; here bacitracin appeared to rank second in activity only to penicillin, whereas it was less active than chlortetracycline and chloramphenicol against pneumococci. The same lot of bacitracin was used in both studies so that the difference in activity of this agent was not a factor.

Differences in the activity of penicillin and streptomycin, especially the former, against the viridans group of streptococci and the enterococci were also noted. The wider variations in the concentrations of these agents required to inhibit different strains are indicated by the slopes and shapes of the curves representing the susceptibility of enterococci to penicillin, suggesting a possible heterogeneity of the strains represented in that curve. This will be seen later to be an important factor in the action on other species.

Differences in the activity of the same antibiotics against various types of pathogenic bacteria can also be readily compared, as was well illustrated, in the antibiotic spectrums against pseudomonas and proteus.[4] Only bacitracin appeared to be equally inactive against all strains of both organisms. The polymyxins, especially polymyxin B, were the most active against pseudomonas, but they were essentially inactive against proteus. Penicillin was inactive against pseudomonas but inhibited a large proportion of the strains of proteus in moderate concentrations. Streptomycin and chlortetracycline appeared to be about equally active against strains of both pseudomonas and proteus although moderately high concentrations of these agents were required to produce inhibition of each and a small proportion of the strains of both species were highly resistant to streptomycin. Chloramphenicol, on the other hand, although slightly less active than chlortetracycline against pseudomonas, was much more active against strains of proteus.

The shape of the curves representing the activity of streptomycin against both proteus and pseudomonas and that of the curves representing the penicillin sensitivity of strains of proteus, as shown here, and of enterococci, as shown previously, indicate that the susceptibility of the same or closely related species to the respective antibiotics may be differentiated. The basis of this phenomenon is not readily apparent. However, two possible explanations may be suggested. The "resistant" strains may be those selected through exposure to the given antibiotic, to a related one, to substances other than antibiotics, or possibly even to certain physical agents that have similar selective properties. It is possible, however, that the separate and distinct portions of the individual curves represent biologically or biochemically distinct groups of strains or separate species that have been lumped together. The former explanation for the curve depicting streptomycin activity seems most likely because of the rapidity with which streptomycin-resistant strains appear during treatment and then persist. The explanation of the shape of the curve representing the penicillin sensitivity of strains of proteus was subsequently clarified, as pointed out below.

The observations made on strains of pathogenic staphylococci isolated at the Boston City Hospital in 1949 and earlier[5] and studied in the same manner offered the first clear indication of the possible usefulness of this method for detecting changes in the susceptibility of micro-organisms to antibiotics under the impact of their extensive use. The antibiotic spectrum of the staphylococcus was first constructed at a time when chlortetracycline and chloramphenicol were first introduced; the latter had only rarely been used, but chlortetracycline was being extensively studied at that time in this hospital. Penicillin, of course, was being given extensively, and streptomycin to a moderate extent, whereas polymyxin and bacitracin were not used at all. The differences in the shape of the curves representing the sensitivity of the staphylococci to the various agents may reflect differences in the extent and duration of their use. However, this was evident only with respect to penicillin.

The curve representing the results of tests for penicillin sensitivity of all the strains of staphylococci that were tested up to that time shows a steep rise, indi-

cating that about half the strains were highly sensitive, being inhibited by concentrations of 0.1 microgm. or less per cubic centimeter; the remainder of this curve, however, rose gently, indicating the wide range of concentrations of penicillin required to inhibit the other half of the strains. A breakdown of the strains into those isolated before 1946 and those isolated later showed that over 80 per cent of the former were inhibited by less than 0.04 microgm. per cubic centimeter whereas only about a third of the latter were equally sensitive. However, there appeared to be no significant difference in this respect between the strains obtained in 1946 and 1947 as compared with those studied during 1948 and 1949.

In another and larger series of staphylococci studied in 1951 and 1952[6] fewer than a fourth of the strains were sensitive to 1 microgm. of penicillin or less per cubic centimeter, and more than two thirds were highly resistant to that agent. The earlier studies had shown the strains isolated in 1948 and 1949 to be fairly uniform in their sensitivity to chlortetracycline, and none were highly resistant to that agent. By 1951 - 52 the curve representing chlortetracycline had a shape similar to that of penicillin — with a similar sharp cleavage between strains that were sensitive and those that were resistant to that agent. About 70 per cent of strains of staphylococci were sensitive, as indicated by the first steep portion of the curve, and almost all the rest were moderately or highly resistant. The curve representing oxytetracycline* paralleled that of chlortetracycline, but it showed that the majority of the strains were somewhat less sensitive to oxytetracycline than to chlortetracycline and there was a larger proportion that were resistant, and to a higher degree, to the former. These strains had all been collected before erythromycin (Ilotycin, Erythrocin) became available, and all were about equally sensitive to that antibiotic.

The distinction between the strains represented in the two ascending limbs of the curve for penicillin was paralleled by the penicillinase-producing property of the strains. The strains that required 12.5 microgm. or more of penicillin per cubic centimeter all produced penicillinase whereas those sensitive to 1.6 microgm. or less all failed to produce the enzyme. Only a few strains in the intermediate zone were inhibited by 3.1 or 6.3 microgm.; some of these did and others did not produce penicillinase.

The foregoing has been only by way of an introduction to the presentation of material collected in the past year in an attempt to determine whether and to what extent the changes in antibiotic resistance of staphylococci to penicillin extended to other common pathogenic bacteria or involved other antibiotics. Additional groups of strains collected and tested in the intervening years may also shed some light on this problem. Observations made in the course of these studies may be of interest for the interpretation of the data collected. However, it has not yet been possible to restudy, on repeated occasions, significant numbers of strains of all the different species of bacteria that are pathogenic, or potentially so, for human beings. The remainder of this presentation is therefore concerned only with a few species that were studied, including most of those that have been given earlier as illustrations of the various types of antibiotic spectrums.

A considerable number of strains of type-specific pneumococci and Group A hemolytic streptococci collected during recent months were tested with all the generally available antibiotics; so far as the antibiotics that were also studied in 1949 and earlier are concerned the results were almost identical in the more recent tests and are not presented in detail. A number of strains of *Streptococcus viridans* and of enterococci were also tested, but their numbers are too few and studies of other characteristics of the strains are still in progress while more are being collected.

Resistance of Staphylococci

In common with many workers in other countries and in other parts of this country, I have been particularly interested in the increasing antibiotic resistance of staphylococci. Since, as already indicated, groups of strains of *Staphylococcus aureus* have been specifically studied at the Boston City Hospital at different times and with various antibiotics, it is of interest to re-examine the data thus accumulated with a view to determining to what extent the phenomenon of increasing resistance applies to antibiotics other than penicillin and, if possible, some of the factors that might be responsible for, or at least associated with, this increase in resistance. The susceptibility to penicillin of 6 groups of strains of *Staph. aureus* collected and tested at different times in the last decade or so is depicted in Figure 1. The three curves representing, respectively, the strains isolated before 1946, those obtained from 1946 through the middle of 1949 and those isolated and tested in the fall and winter of 1951 - 52 show a progressive decrease in the proportion of highly sensitive strains and a corresponding increase not only in the proportion of resistant strains but also in the degree of their resistance to penicillin. A fourth small group of strains isolated and tested late in 1953 is also shown in a curve that does not differ essentially from that representing the 1951-52 strains.

These four curves were constructed from the results obtained during the periods mentioned with strains collected at random from all types of infected materials submitted for culture and yielding *Staph. aureus* as the only or predominant organism. Two selected groups of strains collected by Dr. George G. Jackson in this laboratory are also represented in the same figure. One of the curves depicts the susceptibility of 50 strains of *Staph. aureus* that were the only

*The trade name for oxytetracycline is Terramycin.

or predominant organisms in cultures from 50 of 166 consecutive patients studied at autopsy at the Boston City Hospital in the spring of 1950. During the final illness no antibiotic had been given in 6 cases, chlortetracycline alone in 1, and penicillin in all the others (in combination with either chlortetracycline or oxytetracycline in 3). The sixth curve represents the penicillin sensitivity of 44 strains of staphylococci isolated in 1950-51 from various parts of the alimentary tract, mostly from feces, of patients with staphylococcal gastroenteritis; 5 of these were from patients who had received no antibiotic therapy, and the rest from patients under treatment with either chlortetracycline (16 strains) or oxytetracycline (23 strains) at that time. The last two series of strains contained an even greater proportion that were highly resistant to penicillin; some of them grew uninhibited in mediums containing 6400 microgm. of penicillin per cubic centimeter. The only strains of these two series that were inhibited by less than 12.5 microgm. were obtained from patients who, as far as could be determined, had received no antibiotic treatment during their illness.

The susceptibility to chlortetracycline and oxytetracycline of strains of *Staph. aureus* isolated at different times at the Boston City Hospital is presented in Figure 2. The curves in the lower panel of this figure show that the strains obtained from patients before chlortetracycline was first introduced or during the first few months of its use were more or less uni-

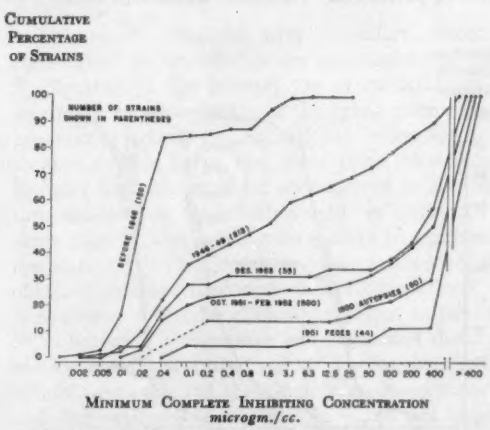
Cumulative Percentage of Strains
Number of strains shown in parentheses
Minimum Complete Inhibiting Concentration microgm./cc.

Figure 1. *Susceptibility of* Staph. aureus *to Penicillin (Strains Isolated at Boston City Hospital).*

form in their susceptibility to that antibiotic, only a small proportion of moderately sensitive strains being encountered. The two series collected during 1951-52 and late in 1953 yielded biphasic curves, the second steep slope representing about a fourth of the strains of each series that were moderately resistant. The 50 strains obtained from the series of autopsies that were mentioned earlier when tested in the same manner also yielded such a curve. However, the 44 strains from patients with staphylococcal enteritis (labeled "fecal strains") contained only a small proportion of moderately sensitive organisms, and more than three quarters of strains were inhibited by only 50 to 200 microgm. of chlortetracycline per cubic centimeter. Most of the more sensitive strains were obtained from patients who had not received any antibiotics in the hospital. The well known instability

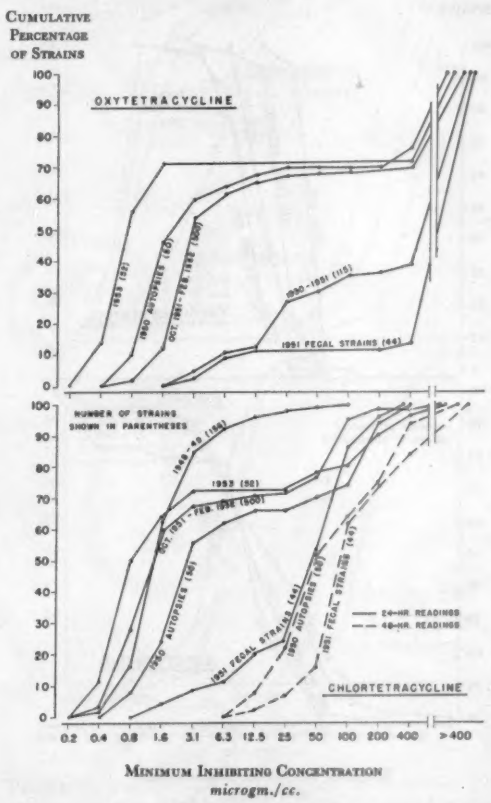

Figure 2. *Susceptibility of* Staph. aureus *to Oxytetracycline and Chlortetracycline (Strains Isolated at Boston City Hospital).*

of chlortetracycline during prolonged incubation at the slightly alkaline pH of the medium used is demonstrated by additional curves depicting the results of the forty-eight-hour readings of the same tests with the last two series of strains. A much wider divergence of the lower portion of the curves of the autopsy as compared with the "fecal" strains probably reflects greater stability of the higher concentrations of chlortetracycline hydrochloride, as suggested by the fact that the upper portions of the curves of the autopsy strains are also much closer to each other than the lower portions of the same curves.

The upper panel of Figure 2 shows the susceptibility of five series of strains of staphylococci to oxytetracycline; four of them correspond to series that

are also depicted in the lower panel and were tested at the same time. Since oxytetracycline is much more stable in these tests, the curves for forty-eight-hour readings are not included. The 1948-49 series shown in the lower panel was studied before oxytetracycline became available and therefore was not tested with

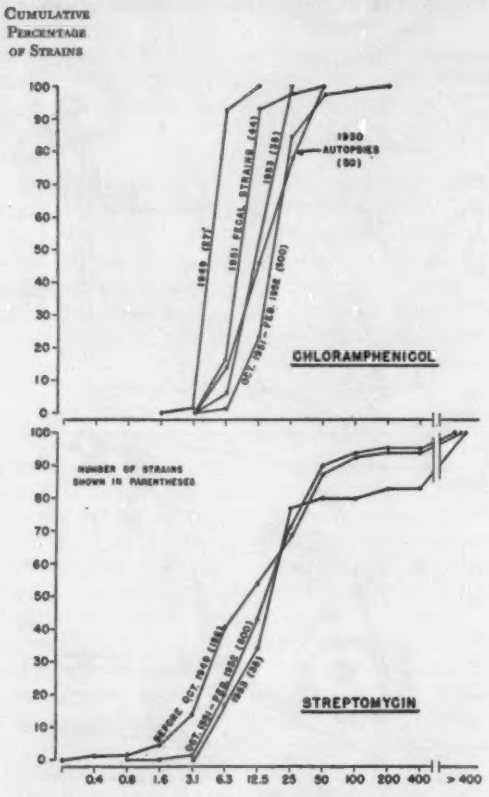

FIGURE 3. *Susceptibility of* Staph. aureus *to Chloramphenicol and Streptomycin (Strains Isolated at Boston City Hospital).*

that agent. A fifth series of strains, however, was tested specifically with oxytetracycline during the period when that agent was being studied intensively and was used in this hospital in preference to other antibiotics. It is seen, first of all, that even among strains of the first series tested — namely, the autopsy series — more than a fourth were highly resistant to that agent. This is assumed to be the result of cross-resistance from chlortetracycline. The three curves representing the three series that were unselected so far as oxytetracycline therapy was concerned were similar in the proportion of strains that were highly resistant to that agent, and although the strains represented in the sensitive portion of the curve of the series collected in 1953 appeared to be somewhat more sensitive than the earlier ones, the difference is probably not significant. On the other hand the strains studied during the clinical trial of oxytetracycline were predominantly resistant, and the only ones among the so-called "fecal strains" that were sensitive to 12.5 microgm. or less per cubic centimeter were from patients who had not received any antibiotics.

Chloramphenicol and streptomycin have had only limited use in this hospital since the introduction of chlortetracycline except in the treatment of certain resistant infections, particularly staphylococcal infections, during the last two years. The upper panel of Figure 3 shows that no staphylococcal strains of moderate or high degrees of resistance to chloramphenicol were encountered in five different series studied at the Boston City Hospital between 1949 and 1953. The apparent differences among these series are probably not significant, or they may represent crossresistance of some of the strains that are moderately or highly resistant to chlortetracycline and oxytetracycline. The lower panel of the same figure shows that only a small proportion of the strains of three different series that were tested with streptomycin were moderately or highly resistant to that agent. Otherwise, there was no great difference in the susceptibility of the different series of strains to streptomycin.

Bacitracin and polymyxin have only rarely been used in this hospital. The susceptibility to these antibiotics of a series of strains is depicted in Figure 4. The two series were similar in the sensitivity of the strains to polymyxin. However, the strains isolated in

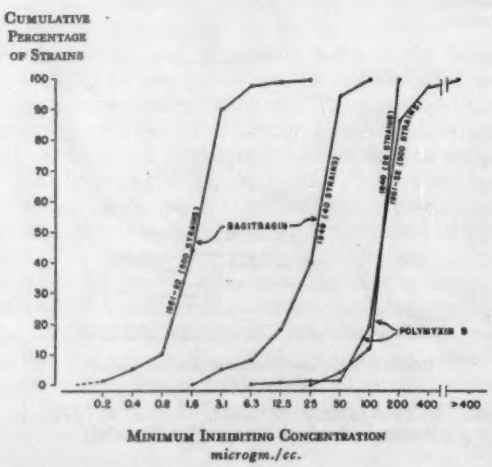
CUMULATIVE PERCENTAGE OF STRAINS
BACITRACIN
POLYMYXIN B
0.2 0.4 0.8 1.6 3.1 6.3 12.5 25 50 100 200 400 >400
MINIMUM INHIBITING CONCENTRATION
microgm./cc.

FIGURE 4. *Susceptibility of* Staph. aureus *to Bacitracin and Polymyxin B (Strains Isolated at Boston City Hospital).*

1951-52 appear to have been considerably more sensitive to bacitracin than those isolated in 1949. The results have all been expressed on a weight basis, but the variations in assayed potency of the respective lots used in the two studies can account for only a minor part of these differences. The lot used in the

early studies was assayed at 34 units per milligram as compared with 44 units per cubic centimeter for the one used in 1951-52. Two possible explanations may be offered for the differences in the results obtained with bacitracin in the two series of staphylococcal strains. The first is that bacitracin, like other polypeptide antibiotics, is not clearly defined chemically, and different lots may vary considerably in purity, chemical composition and rate of decay; this may be reflected, in turn, in differences in the activity of various lots against any given species. Secondly, the sensitivity of strains to bacitracin may be increased as a result of exposure to other antibiotics in vivo. Both these explanations are subject to verification, but adequate data to determine their validity are not available at present.

Resistance of Gonococci

Two or more series of strains of gonococci were collected and tested at different times with some of the antibiotics and with sulfadiazine.[7,8] All the strains were isolated from exudate of the male urethra or the female cervix of patients with acute gonorrhea in the Genito-Urinary Out Patient Clinic at the Boston City Hospital. All the patients were treated with penicillin, either immediately after or a few days before these strains were obtained, except for one series of strains that was collected during 1948 and tested with chlortetracycline in the course of a special study on the efficacy of that agent in the treatment of gonorrhea in males.

The results obtained with penicillin, chlortetracycline and oxytetracycline are summarized in Figure 5. Because of the general use of penicillin in the treatment of gonorrhea and the great interest in the question of whether gonococci are increasing in resistance to that agent, the lower panel of this figure includes the only material encountered in the literature and dealing with studies made in essentially the same manner and lending themselves to similar representation.[9,10] The gonococci in the latter study were obtained in three successive years from patients who were considered to be clinically resistant to penicillin or in whom the organisms were obtained during or after treatment with that agent. The workers in Düsseldorf who collected these data considered that they had demonstrated a statistically significant increase in the resistance — or rather a decrease in the proportion — of the more sensitive strains in the successive series because the same materials and methods were used throughout. However, considering the fact that they used a serial twofold-dilution method similar to that employed in this laboratory, the three series may be considered as showing no important differences.

The results obtained in four separate series of strains isolated and tested with penicillin at different times in this laboratory are depicted in the upper panel of Figure 5. Although three of these series — namely, those collected in 1945, 1947 and 1949 — show apparently progressive increases in resistance of a degree about the same as or even greater than those noted by the German workers, these changes, too, are not considered to be significant. Moreover, in spite

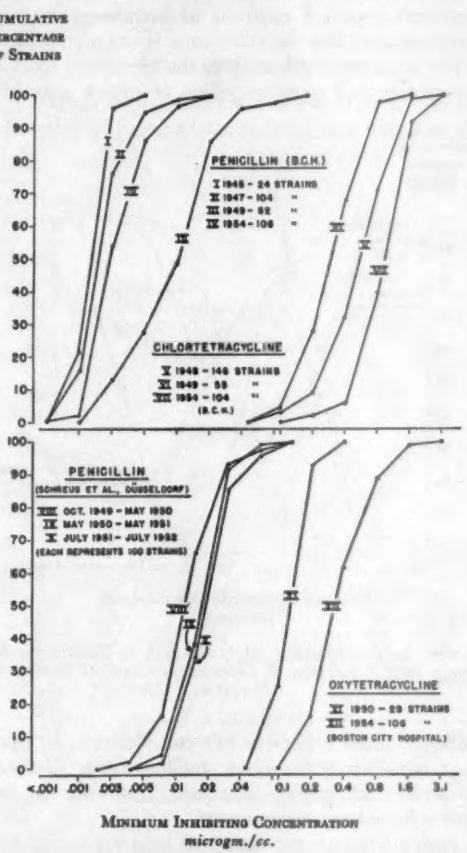
Cumulative Percentage of Strains
PENICILLIN (B.C.H.)
I 1945 - 34 STRAINS
II 1947 - 104 "
III 1949 - 88 "
IV 1954 - 106 "
CHLORTETRACYCLINE
I 1948 - 146 STRAINS
II 1949 - 88 "
III 1954 - 104 "
(B.C.H.)
PENICILLIN
(SCHREUS ET AL., DÜSSELDORF)
III OCT. 1949 - MAY 1950
II MAY 1950 - MAY 1951
I JULY 1951 - JULY 1952
(EACH REPRESENTS 100 STRAINS)
OXYTETRACYCLINE
II 1950 - 29 STRAINS
III 1954 - 106 "
(BOSTON CITY HOSPITAL)
<.001 .001 .003 .005 .01 .02 .04 0.1 0.2 0.4 0.8 1.6 3.1
Minimum Inhibiting Concentration
microgm./cc.

Figure 5. *Susceptibility of Gonococci to Penicillin, Chlortetracycline and Oxytetracycline (Strains Isolated at Boston City Hospital, with Comparable Data Reported by Schreus et al.[9,10]).*

of the continued intensive use of penicillin since 1949, the results obtained in the last series, which was collected in 1954 and tested by the same method as that used in 1949, more nearly resembled those obtained in the earlier series.

In a previous presentation of some of the earlier data[7] the possibility of a decrease in the penicillin sensitivity of gonococci was considered, but the changing character of penicillin and some differences in the methods employed were also mentioned as possible explanations for the differences observed. Presumably, no such changes in the character of penicillin have occurred since 1946, when highly purified crystalline penicillin G came into general use. Moreover, although the proportion of strains obtained during or after penicillin administration, as compared with

those obtained in untreated patients, may have varied in the different series, this could not have affected the results because strains obtained before any treatment was given were no more sensitive than those that apparently persisted in the face of penicillin administration. In the 1954 series[8] the strains obtained before treatment appear if anything to have been somewhat more resistant, but the difference is not significant.

The apparent difference in the sensitivity to chlortetracycline and oxytetracycline of strains isolated at

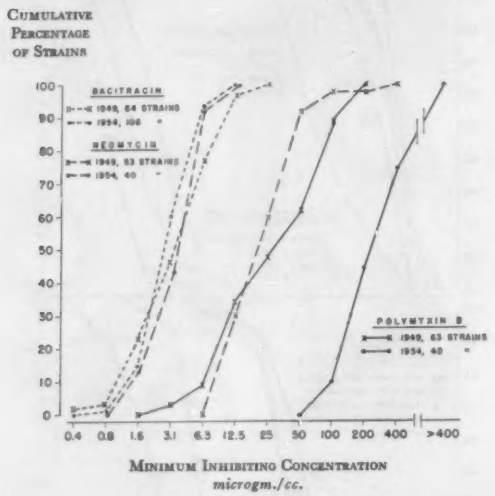

FIGURE 6. *Susceptibility of Gonococci to Bacitracin, Neomycin and Polymyxin B (Strains Isolated at Boston City Hospital).*

different times is likewise not considered to be significant considering the crude method used. Certainly, no strains of greatly increased resistance to these agents have been encountered.

Figure 6 shows the results of tests for sensitivity to bacitracin, polymyxin and neomycin of two series of strains of gonococci, one collected in 1949 and the other in 1954. None of these antibiotics had been used in the treatment of any of the patients from whom these strains were isolated, nor is indirect contact with these antibiotics at all likely. The results obtained with bacitracin in the two series were essentially the same, whereas those obtained with the other two agents were significantly different. The differences in the susceptibility of the gonococci to these antibiotics were quite contradictory; the 1954 series appeared to be considerably more resistant than the 1949 series to polymyxin but the reverse was true of neomycin. Here, again, the variability of the polypeptide antibiotics manufactured and supplied in different years and the variable effects of the widespread use of different antibiotics are possible explanations of these differences; these influences need not, of course, work in the same direction.

The results of tests with chloramphenicol, streptomycin and sulfadiazine on the same two series of strains of gonococci are depicted in Figure 7. No differences were noted in the sensitivities of the strains of the two series to either chloramphenicol or streptomycin although their susceptibility to sulfadiazine was strikingly different. Less than 80 per cent of the strains isolated in 1954 were inhibited by 50 microgm. per cubic centimeter (5 mg. per 100 cc.) or less, whereas only 8 per cent of the strains isolated in 1949 were inhibited by this concentration and more than 80 per cent of the earlier strains were not inhibited by 100 microgm. per cubic centimeter; indeed, about two thirds of the last group of strains grew freely in a medium containing 400 microgm. per cubic centimeter. These results obviously suggest the possibility that during the long period since penicillin has almost completely replaced the sulfonamides in the treatment of gonococcal infections, the gonococci have regained their sensitivity to those agents. The results obtained in 1954 correspond to those reported by other workers early in the sulfonamide era.

Resistance of Meningococci

There is also considerable interest, both theoretical and practical, in the relative susceptibility of menin-

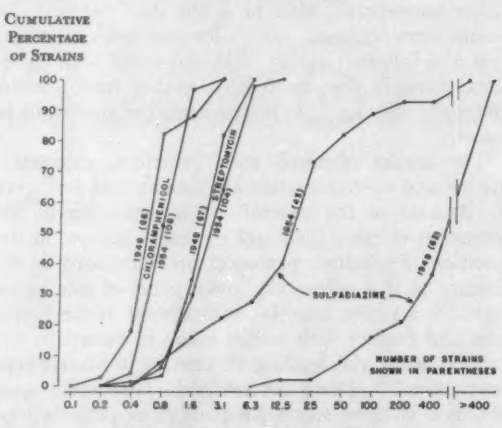

FIGURE 7. *Susceptibility of* Neisseria gonorrhoeae *to Antimicrobial Drugs (Strains Isolated at Boston City Hospital).*

gococci to penicillin and to sulfonamides and particularly in the question of whether strains of increased resistance to these agents, particularly to sulfonamides, are now causing human infections. Unfortunately, no early data in this laboratory are available for comparison except for a number of strains that were tested with penicillin in 1944 and 1945.[11] When these results are compared with those obtained in a group of recently isolated strains of meningococci tested during the last year (most of them furnished by Dr. Sara E. Branham), there appears to be some increase in the penicillin resistance of the strains.[12]

The difference, however, is probably not significant and may be within the limits of error of the method or perhaps associated in part at least with changes in the character of penicillin available in the two periods.

Tests of the susceptibility of the recent strains to sulfadiazine indicated that all but 6 of the 50 strains were completely inhibited (after incubation for forty-eight hours in sulfadiazine-containing blood agar) by 50 microgm. per cubic centimeter (5 mg. per 100 cc.). Unfortunately, results with earlier strains tested with sulfadiazine in the same manner are not available for comparison. Moreover, some question may be raised regarding the 6 strains that were found to be most resistant to sulfadiazine and required 200 or 400 microgm. per cubic centimeter to produce inhibition; protection tests with these strains, carried out in mice by Dr. Branham and reported in a personal communication, suggested that they were as susceptible in this test as the strains that were highly sensitive in the in vitro tests, in which the slow growth of the organism required incubation for forty-eight hours and a large inoculum was used.

Resistance of *H. Influenzae*

Strains of *H. influenzae* were collected and tested in 1949[2] and again in 1954,[13] but numbers sufficient to permit comparisons are available only in the tests with penicillin, streptomycin and chlortetracycline (Fig. 8). No strains of greatly increased resistance to any of these agents were encountered. The strains isolated in 1954 appeared to be more sensitive to penicillin and more resistant to streptomycin and to chlortetracycline. The differences can hardly be considered to be significant particularly in view of the inherent errors of the method and the facts that with this species as with gram-negative cocci the strains were incubated for forty-eight hours before the results of the tests were read and that these tests were done at different times.

Resistance of Pseudomonas

The most detailed comparison was possible with the strains of pseudomonas.[14] In this instance 30 strains isolated in 1949, which had been preserved in the lyophilized state, and 103 others isolated in 1954 were studied intensively and found to be typical of the species *Pseudomonas aeruginosa*. All were then tested at the same time with each of ten antibiotics. The recent strains were found to be similar to the earlier ones in their sensitivity or resistance to polymyxin, erythromycin, chloramphenicol, bacitracin, penicillin and also, interestingly enough, to oxytetracycline. There was a definite increase in the resistance to streptomycin of the strains isolated in 1954, a much higher proportion of them being highly resistant to that agent. There was also a significant decrease in the sensitivity of the 1954 strains to neomycin; this may be a reflection of crossresistance to streptomycin but could not be due to changes in the antibiotic since all strains were tested with the same lot at the same time. There was also an increase in resistance of the recent strains to chlortetracycline, and accompanying this was an appreciable increase in resistance to tetracycline. All the earlier strains, of course, were isolated in 1949 before either oxytetracycline or tetracycline had been introduced.

Resistance of Proteus

Finally, comparisons are also available of two series of strains of proteus, one isolated and tested in 1949

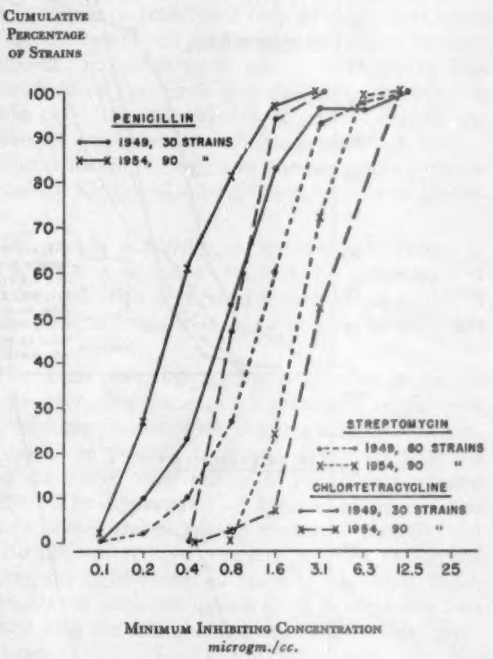

Figure 8. *Susceptibility of* H. influenzae *to Three Antibiotics in Vitro (Strains Isolated at Boston City Hospital).*

and the other in 1954.[15] The study of the recent strains, however, revealed an important effect of species differences on the susceptibility of proteus to the different antibiotics. The criteria used for classification into species were those of Rustigian and Stuart.[16] Strains that failed to produce indole were classified as *Proteus mirabilis*. They behaved differently from all the other species, which resembled each other more closely in their susceptibility to antibiotics; it was therefore convenient to lump the strains other than those of *P. mirabilis* together for the purpose of comparisons.

When this was done with the strains isolated in 1954 it was found that, whereas most of the strains of *P. mirabilis* were inhibited by penicillin in concentrations of 100 microgm. or less per cubic centimeter, almost all the strains of other species grew uninhibited in a concentration of 400 microgm. Contrari-

wise, almost all the strains of *P. mirabilis* were resistant to 400 microgm. of oxytetracycline or chlortetracycline per cubic centimeter and required 100 or 200 microgm. of tetracycline per cubic centimeter for inhibition; two thirds of the strains of the other species were inhibited by 12.5 microgm. or less of each of the three tetracyclines. The strains of all species appeared to be about equally susceptible to neomycin, but whereas strains of *P. mirabilis* were about as susceptible to streptomycin as to neomycin, more of the strains of species other than *P. mirabilis* were highly resistant to streptomycin. The strains of *P. mirabilis* were also somewhat more susceptible than the others to chloramphenicol.

These findings reduce the validity of any comparisons that may be made with the results of the sensitivity tests done on the strains isolated and studied in 1949, which were not differentiated according to species. In Figure 9 all the strains of proteus isolated and tested in 1949 are compared with those isolated and tested in 1954, the strains of all the species being lumped together, and comparisons are shown for four different antibiotics. The results obtained in 1954 are also broken down into those obtained with the strains of *P. mirabilis* and those obtained with the other three species lumped together. Most of the differences could be explained in part at least by the assumption that the more recent series contained a significantly larger proportion of strains of *P. mirabilis* than the earlier series did.

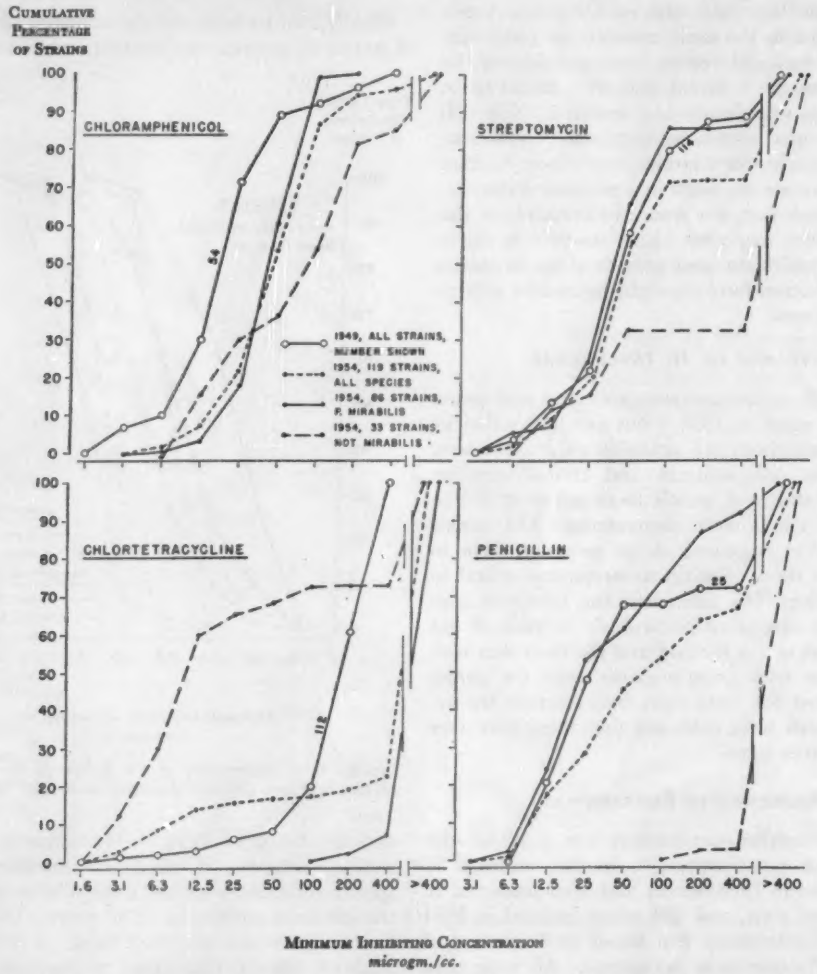

FIGURE 9. *Susceptibility of Proteus to Four Antibiotics (Strains Isolated at Boston City Hospital).*

DISCUSSION

The changing patterns of resistance of bacteria to antibiotics may be summarized. The number of resistant strains of *Staph. aureus* and the degree of resistance to penicillin and to a lesser extent to chlor-

tetracycline and to oxytetracycline have shown a definite increase. Much of the resistance to oxytetracycline that was observed when this agent first became available may well have been a reflection of crossresistance from chlortetracycline, but the markedly greater prevalence of strains resistant to oxytetracycline among those isolated from patients under treatment with that agent and from patients with staphylococcal enteritis during treatment with either oxytetracycline or chlortetracycline must be related to the therapy with these agents.

No important changes in resistance to any of the antibiotics have thus far been definitely authenticated in this hospital for pneumococcus, group A hemolytic streptococcus, meningococcus, gonococcus, *H. influenzae* and proteus. There appears, however, to have been a definite increase in the sensitivity to sulfadiazine of strains of gonococcus isolated in 1954 as compared with those isolated in 1949.

The appearance of and rapid increase in erythromycin-resistant staphylococci during the intensive use of this agent and the subsequent decline in frequency when the use of the agent was discontinued was reported at last year's Antibiotic Symposium by Lepper and his co-workers.[17] Kirby and Ahern[18] have also described a decline in the prevalence of chloramphenicol-resistant staphylococci during a period of two years after the use of that antibiotic had been greatly curtailed in their wards.

There appears to be a definite increase in resistance of strains of pseudomonas to streptomycin and the broad-spectrum antibiotics and possibly also to neomycin. The last may be a manifestation of crossresistance from streptomycin, and the increases in resistance to chloramphenicol and to tetracycline are probably the result of crossresistance from chlortetracycline and oxytetracycline, since neither chloramphenicol nor tetracycline had been used to any great extent before these strains were isolated.

The material presented may also be summarized from the point of view of the individual antibiotics. In spite of the intensive use of penicillin, both within and outside hospitals, increases in the frequency of resistant strains of bacteria and in the degree of their resistance have been completely authenticated at the Boston City Hospital only for the staphylococcus. Some increase in penicillin resistance of strains of proteus was noted, but this may have been the result of differences in the distribution of species within the two series of strains that were compared. The proportion of strains resistant to streptomycin in several species, notably *Ps. aeruginosa,* has risen. That this has not been more striking may be due to the limited extent to which this antibiotic has been used and also to the fact that its administration here has for several years been restricted to combinations with other effective antimicrobial drugs.

Chlortetracycline and oxytetracycline have been noted to be less effective, particularly against staphylococci, but whereas strains of *Ps. aeruginosa* appeared to have increased in resistance to the former, there does not seem to have been a corresponding increase in their resistance to oxytetracycline.

Striking changes in resistance of staphylococci to erythromycin correlated with its intensive use within another hospital have been reported by Lepper and his co-workers.[17] Such changes have been avoided in this hospital by the use of erythromycin only in combination with other effective agents.

Chloramphenicol has had only limited application within this hospital, and neomycin, bacitracin and polymyxin have been used only in occasional cases. Major changes in the sensitivity or resistance to these antibiotics have not been noted. Such changes as were observed may have been due to the use of other antibiotics. The increase in the sensitivity of the strains of staphylococci to chloramphenicol after a drastic reduction in its use at another hospital, as reported by Kirby and Ahern,[18] is of interest in this regard.

The greater sensitivity of strains of gonococcus to sulfadiazine is probably real, but the significance of the demonstration of a small proportion of strains of meningococci resistant in vitro to this agent is not clear.

The data presented suggest a number of factors in the changing patterns of resistance of bacteria to antibiotics. Some of the changes may reflect crossresistance or possibly increased sensitivity resulting from the use of other related or seemingly unrelated agents. The importance of species differences was clearly demonstrated among strains of proteus, and similar differences have been seen among streptococci. Among strains of *Staph. aureus* isolated from patients, resistance to penicillin appears to be completely correlated with the ability of the strains to produce penicillinase.

Most of the important changes that have been noted, however, appear to be directly correlated with the extensive use of the particular agent or agents involved, as clearly indicated by the data concerning increased resistance of staphylococci to penicillin, chlortetracycline and erythromycin. However, there have been some apparent changes in the sensitivity or resistance of some organisms to antibiotics that have not been used. With neomycin, the possibility of crossresistance from streptomycin had been mentioned, but with this antibiotic and with the polypeptides, bacitracin and polymyxin, the changes may be related to differences in the purity or composition of the lots of antibiotics used at different times. However, the possibility of changes in sensitivity to these agents resulting from the extensive use of other antibiotics cannot be entirely eliminated since such changes have been noted in studies carried out in vitro.

The implications of these observations concerning the effect of intensive use of antibiotics on resistance may seem obvious when considered in the light of the

observations on the staphylococci, particularly those reported by Lepper and his co-workers.[17] The well known increase in resistance of gonococci to sulfonamides after they had been extensively used for some time and the apparent return of sulfadiazine sensitivity in recent years after the use of sulfonamides had declined seem to support such a correlation. The occurrence and increase in prevalence of streptomycin-resistant strains of several bacterial species during the administration of these agents can also be readily demonstrated.

These data, however, do not entirely clarify the problem of the origin of the resistant strains derived from patients. Nor do they shed light on the basis for the difference in the resistant strains of staphylococci obtained from patients, all of which produce penicillinase, and those derived from sensitive strains in vitro as the result of continued exposure to increasing concentrations of penicillin, which do not produce the penicillin-inactivating enzyme. Nor do they explain why significant changes in resistance to the most widely used antibiotics have not been noted in some of the most common species of bacteria, in spite of the fact that resistant strains can readily be derived by repeated exposures of such bacteria to the same antibiotic, in vitro.

Similar studies bearing on changes in antibiotic resistance of pathogenic bacteria reported by others are not within the scope of this paper. It may be pointed out, however, that results have varied widely. For example, one report from New York City[19] suggests that there were significant increases in resistance in almost all species, including beta-hemolytic streptococci, to each of five widely used antibiotics. On the other hand, a study from Paris,[20] carried out during the same period, showed significant and progressive changes only in the staphylococci. Some of the observations presented here may serve to point up the difficulties in reconciling such diverse findings.

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MEDICAL PROGRESS

MEDICAL ELECTRONICS

LEE B. LUSTED, M.D.*

SAN FRANCISCO

THE large number of medical electronic devices developed in the past year indicates a rapid expansion of this field. Electronic instruments are important medical tools.

Electric phenomena in the human body had long been of interest, but the low signal amplitude made study difficult. After De Forest's development of the triode vacuum tube in 1907, electronic equipment was built to amplify the weak electric signals from the heart and central nervous system, and subsequent advances in electronic technics were applied to problems in various medical fields.

About 1932 the American Institute of Electrical Engineers gave formal recognition to the problems of electronic instrumentation in medicine and biology when its committee on therapeutics sponsored a dis-

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cussion on electromedical problems. Because of interest in medical electronics, the national Conference on Electrical Techniques in Medicine and Biology has been held annually for seven years under the sponsorship of the Institute, the Institute of Radio Engineers and the Instrument Society of America.

The professional group on medical electronics that the Institute of Radio Engineers formed in April, 1952, now has, among its more than 1000 members, electronic engineers, members of the medical profession, biologists, physiologists, biophysicists and physicists, all of whom are interested in the application of electronic technics to medicine and biology.

Some electronic devices used in medical science and in clinical medicine are presented in this article.

Laboratory Devices

Electronic amplifiers and electronic stimulators are familiar pieces of laboratory equipment. Among the many new types of electronic laboratory devices now in use are electronic impulse counters, called scalers, which are used with Geiger–Müller tubes to measure the activity of radioactive materials. Guyton et al.[1] have adapted an instrument of this type to make a continuously recording hemoglobinometer.

The multiplier phototube is the pickup device for instruments that measure an amount of light; the spectrophotometer, the densitometer and the flame photometer are examples. Light falling on the photocell causes a tube current to flow that is amplified by an intermediate circuit and recorded.

Scintillation counters, used to detect radioactivity, are constructed with a crystal and a multiplier phototube — a tube so constructed that when a small amount of light strikes the photosensitive surface the secondary electrons emitted are increased in number within the tube, so that an amplification of 2×10^6 is possible. When the crystal is struck by radiation it emits a small amount of light. The multiplier phototube amplifies the photoelectrons, which, after further electronic amplification, are recorded by a mechanical counter. Very high counting rates may be obtained with the scintillation counter.

Television engineering technics have been applied to tissue-cell and blood-cell counting. Mellors and his associates[2,3] have developed a microfluorometric scanner designed for the automatic detection of cancer cells in smears of exfoliated cells obtained from tissue secretions and spread on a microscope slide. An early type of television scanning disk, an ultraviolet light source, a photocell pickup tube and the appropriate electronic counting circuits are used to count cells taking up a fluorochrome stain. Cancer cells take up more of the fluorochrome stains than normal cells do and are thus differentiated from normal cells. This type of device shows promise in the rapid counting of a large number of exfoliative-cell smears, or in other special cases in which many cells must be counted. With this method the nerve cells in the spinal cord could be counted from thin serial sections of the entire cord.

Television scanning technics are used to count and record the number of red blood cells or white blood cells in a counting chamber. Another instrument, which can count blood cells automatically and is able to compensate for a wide range of variation in all diameters, uses light diffraction through a highly diluted suspension of blood. The diffracted light striking the surface of a phototube activates a dial that gives the blood-count reading.

Diagnosis

Transducers[4,5] (devices used to convert energy of one type to energy of another type) are used to pick up information from the body and convert it to electric energy that can be amplified and recorded. An important part of any medical electronic instrumentation project involves the selection of a transducer. The strain gauge and the thermocouple are examples of transducers used with medical electronics instruments.

Strain Gauge

The strain gauge is an instrument used to translate mechanical force, weight, fluid pressure or displacement into electric energy.[6] A resistance wire is the important part of a strain gauge. Stretching of the wire causes a change in the wire resistance. This wire forms a portion of a balanced electric circuit. Changes in balance voltage that result from a change in length of the resistance wire are amplified by a special type of amplifier and recorded with electrocardiographic apparatus.

Examples of the medical uses of strain gauges are the measurement of arterial and venous blood pressure,[7,8] intrauterine pressure, cerebrospinal-fluid pressure and differential pressures in a pneumotachograph.

Thermocouple

A thermocouple offers a convenient and practical means of body-temperature measurement. Two dissimilar metal wires are joined to form a thermoelement. When two such junctions are kept at different temperatures a voltage is generated. One thermocouple junction is readily attached to the skin,[9,10] and, when the thermocouple voltage is amplified, a meter reading is obtained that indicates the temperature of the skin.

Cardiovascular System

Human electrocardiography[11] began in 1903 with the use of Einthoven's string galvanometer, and since then no system of the body has been investigated as extensively with electronic instruments as the cardiovascular system. Careful circuit analysis[12] and the use of small component parts have resulted in an efficient, compact electrocardiographic unit.

After triode amplifying tubes were developed, high-gain, direct-current amplifiers were used to amplify and record electric cardiac activity. Improved tube types and alternating-current amplifiers soon followed, and heart sounds could be recorded concurrently with the electric activity of the heart. The vectorcardiogram,[13] which has supplemented the electrocardiogram, requires additional electronic equipment to present the cardiac electric vector on an oscilloscope. Hollman[14] has suggested that further development may give a three-dimensional vectorcardiograph.

Ballistocardiography. The ballistocardiograph[15] is an instrument that records the recoil movements of the body resulting from the expulsion of blood from the heart. Information concerning cardiac function is obtained by study of this motion imparted to the body.

Dock et al.[16] recently described a ballistocardiograph that uses magnetic pickup and an electrocardiographic instrument. A small coil of wire is attached to the patient's ankles, and a magnet, placed near the coil, is fastened to the table top. The electric signal induced in the coil as a result of body movement is amplified and recorded by the electrocardiographic instrument. Rappaport and his associates[17] and Gubner, Rodstein and Ungerleider[18] have thoroughly discussed the use of ballistocardiography and its physical considerations; conservation of momentum is the basic physical principle involved.

Blood-pressure-recording devices. Many types of instruments have been suggested for the continuous recording of blood pressure in the arm or leg. For indirect measurement, a pickup device, usually a capacitor microphone, is placed under a blood-pressure cuff, and the systolic and diastolic sounds are recorded with an electrocardiograph. A strain-gauge amplifier and strain gauge attached to a catheter are used to measure accurately and directly the intravascular and intracardiac blood pressure. Landsman[19] has described the use of a strain-gauge amplifier to record simultaneously the systolic and diastolic blood pressure, and Noble's[20] book gives a thorough analysis of present blood-pressure-recording methods.

Blood-flow-recording devices. To record total systemic blood flow Sarnoff and Birklund[21] have used a Potter electroturbinometer, a small rugged turbine that is placed in the blood stream. The blood flow causes the turbine to rotate, and the number of rotations per unit time of the turbine magnet is recorded on a veeder-root counter mounted in the intermediate electronic system. Kolin's[22] technic for measuring blood flow also requires direct access to blood vessels, but does not use blood-vessel puncture. A cuff is placed about an artery, and blood flow is measured by electromagnetic induction. Kalmus[23] has suggested another method for blood-flow measurement that uses two cuffs placed about an artery. One cuff acts as a transmitter, and the other as a receiver for the electric pulses transmitted with and against the direction of blood flow. The pulses increase in velocity when transmitted "downstream" and decrease when transmitted "upstream." The velocity of blood flow can be determined by the difference between these two velocities.

Electronic mapping. Goldman et al.[24,25] have demonstrated a new method of studying the electric activity of the heart. Sixteen or more electrodes of conventional electrocardiographic type are placed in array over the left anterior aspect of the chest from the sternum to the midaxillary line. The signals picked up by the electrodes are amplified and displayed on an oscilloscope that has a tube face divided into a grid pattern corresponding to the position pattern of the leads on the chest. By electronic means, the light intensity of each square on the oscilloscope screen is made proportional to the instantaneous voltage of the corresponding electrode on the chest. As the potential at an electrode rises and falls, the brightness of the corresponding square rises and falls in exact synchronism with it. Through this method it is possible to visualize movements of electric activity across the surface of the heart, instead of analyzing curves obtained from individual points on the chest and limbs.

Electrokymography. The electrokymograph, an instrument for recording motion of the heart border as outlined by the x-ray fluoroscope,[26] employs a roentgen-ray pickup device that, when properly placed over the roentgenoscopic cardiac silhouette, translates the motion of the silhouette border into a varying electric current.

On the x-ray fluoroscopic screen the heart is seen as a dark area against the light background of the lungs. The expansion and contraction of the heart causes the margin of the silhouette to pulsate. To record this pulsation a multiplier phototube housed in a lead case is mounted in front of the fluoroscopic screen. The photosensitive surface of the multiplier phototube looks at an open area, 5 by 20 mm., in the lead shield. This slot is positioned by the use of the fluoroscope so that the long axis is perpendicular to the heart border. As the heart beats, the amount of light coming through the slot varies, depending on the position of the heart border. The output of the multiplier phototube is recorded with an electrocardiographic apparatus.

Central Nervous System

The electroencephalograph is an instrument for recording the electric activity of the brain.[27,28] Because of the low signal strength from the brain — 2 to 1000 microvolts — an electroencephalographic amplifier with a gain of about 10,000,000 is needed. The amplifier must work well in the low frequency range of brain waves — that is, 1 to 100 cycles per second. Careful amplifier construction is needed to meet these requirements, and advances in electronic circuit design

and component construction have resulted in improved electroencephalographic equipment.

Localization of brain tumors. Ultrasonic frequency technics have been used to locate brain tumors. Ballantine et al.[29] have used a direct transmission technic. A water bath was placed around the skull, and electromagnetic waves of ultrasonic frequency were transmitted from a crystal transmitter unit in the water bath through the skull and brain to a receiver crystal on the opposite side of the head. The plot of the received signal demonstrated the outline of the ventricles. This project was recently terminated when thorough investigation had demonstrated that brain tumors could not be well localized by this method because the interference with the ultrasonic beam as it passed through the skull proved excessive.

In an attempt to locate tumors of the brain and other soft tissues Reed and Wild[30] have used a reflected ultrasonic pulse technic, but the strong echo returned by the skull makes it difficult to locate brain tumors by this means. However, tumors in soft tissue have been more easily outlined.

A radioactive mapping technic has been used in brain-tumor surgery to demonstrate the extent of the tumor.[31] Radioactive potassium, which showed greater concentration in tumor tissue than in normal tissue, was given to the patient before operation. A 2-mm. probing Geiger–Müller counter and portable battery-operated counting-rate meter developed by Robinson[32] were used at the time of craniotomy to outline the position and extent of deep cerebral tumors. The 2-mm. Geiger–Müller probe was passed into the brain tissue, and counting rates from different brain areas and at several tissue depths were compared.

Localization of brain tumors with positron-emitting isotopes has been investigated.[33,34] The possibility of better resolution for tumor localization is offered with the coincidence-counting technic than with a single-detector probe or external measurements of gamma emitters.[35] A positron is a short lived nuclear particle that readily combines with an electron. When the combination occurs, two gamma rays are given off that are directed approximately 180° apart. These two gamma rays, which may be detected simultaneously, are responsible for the improved resolution of tumor localization.

Lead-shielded scintillation counters were mounted collinearly on a movable platform, the patient's head was placed between the two detectors, and then successive scans of the head were made. Radioactive arsenic, which has a higher concentration in tumor cells than in normal cells, was used as a positron emitter. Pulses from the detectors were amplified and introduced to a coincidence circuit. The output of the coincidence circuit was connected to a scaler that was used to actuate a printer. Only coincident counts are printed. The scanning maps showed symmetrical counts in normal brain areas and a concentration of counts in the tumor region.

Audiometer. The tone device used to test hearing is an electronic audio-oscillator.[36] The oscillator output (a pure sine wave) is calibrated in terms of the normal hearing level at each frequency, and the amount of hearing loss is indicated either as a percentage of normal or in decibel units. Air and bone conduction can be readily tested with the modern audiometer because of its stable and well calibrated circuits.

Other applications of electronic devices to the nervous system include: the use of electronic circuits as models for studying nervous-system function,[37] and the use of electronic devices as sensory prostheses, as suggested by Wiener.[38]

Other Electronic Devices Used in Diagnosis

Phototimer. Phototimers[39,40] are used on x-ray radiographic, x-ray fluoroscopic and x-ray photofluorographic units. In x-ray equipment, phototimers automatically control the length of the film exposure. The multiplier phototube (a special type of phototube) receives light from a fluorescent surface activated by the x-ray. The phototube circuit has been calibrated in terms of the amount of x-ray needed to give optimum film exposure, and when the photocell has received the required amount of light during an x-ray exposure it activates an electronic circuit that terminates the exposure.

Oximeter. This ingenious device is used to measure the oxygenation of the arterial blood. Photocells are attached to the ear lobe in a small earpiece.[41] The spectral transmission characteristics of hemoglobin are used to measure and to follow continuously the arterial oxygen saturation.

Foreign-body localizer. Berman and Moorhead[42] have applied the principle of the electromagnetic mine detector to a device for localizing metallic particles within the body. Wire coils at the end of a small probe form a balanced electric system connected to a high-gain amplifier and meter. A meter reading shows the imbalance in the circuit caused by a small piece of metal in the magnetic field of the coils. As the probe approaches the metal, the meter deflection increases rapidly. The detecting range of metallic particles is approximately ten times the diameter of the fragment.

Electronic thermometer. An electronic clinical thermometer, which is used like an ordinary thermometer, has been developed. Current from a flashlight battery is passed through metal oxides that are imbedded with wires in the glass rod. The oxides change resistance in precise ratio with the body temperature and give the temperature, accurate to a tenth of a degree, in a five-second period.

Therapy

Cardiovascular System

Wiggers[43] found that ventricular fibrillation in the dog heart could be stopped by placing large metal electrodes directly onto opposite surfaces of the heart and giving shocks of 110 volts, alternating current, with a current of 1 or 2 amperes for about half a second. Guyton and Satterfield[44] used 110 volts, alternating current, to defibrillate a dog's heart through the unopened chest. At least three clinical defibrillator (stimulator) instruments now on the market will deliver a shock of a preset voltage amplitude and duration.

Callaghan and Bigelow[45] showed that electric shocks given on the chest wall of dogs would keep the heart beating regularly. Zoll[46] has demonstrated that cardiac rhythm in human beings may be maintained by application of electric shocks at regular intervals across the anterior chest wall. In fact, in a patient with Stokes–Adams syndrome, a regular heart beat was so maintained for seventy-four hours until spontaneous cardiac rhythm was established. Instruments that combine the cardiac defibrillator and the cardiac electronic pacemaker in a single piece of equipment have been designed,[47] and several models are commercially available.

Central Nervous System

Electrophrenic respirator. Sarnoff and his associates[48,49] have used rhythmic electric stimuli to control respiration. In certain cases of bulbar poliomyelitis in which it may be impossible to place the patient in a tank respirator, regular electric stimuli applied to one or both phrenic nerves can take over the patient's respiration until he is able to go into the respirator, or until his respiratory center is again able to take control.

Electric pulses are supplied from an electrode placed directly over the phrenic nerve in the lower neck. The stimulating current, derived from an electronic stimulator set at a frequency of 40 pulses per second and a pulse duration of 2 milliseconds, is run through a rotating potentiometer that varies the voltage rhythmically. This causes the diaphragm to contract and relax just as it does during spontaneous breathing. This system can also be used to control respiration during general anesthesia.

Hearing aids. One of the most recent developments in electronics, the transistor, has been used in hearing aids. The transistor is a small crystal that may act as an amplifier but requires less power than an amplifier tube. Transistors have made it possible to reduce the weight and size of hearing-aid equipment so that an apparatus that uses three transistors, with batteries, weighs about 100 gm.

Diathermy equipment. Medical diathermy is the use of high-frequency currents to produce heat in the body tissues for therapeutic purposes.[50]

Ultrasonic diathermy and microwave diathermy have recently been introduced. Ultrasonic diathermy equipment[51] is operated at a frequency of about 8×10^5 cycles per second, a higher frequency than the conventional or long-wave diathermy. The acoustic energy is applied to the tissue by a transducer, usually a crystal. The tissue effects of ultrasonic radiation are due either to cavitation in the presence of dissolved gases or to conversion of acoustic energy to heat energy.[52]

Microwave (short-wave-length) diathermy[53] uses the magnetron oscillator tube developed during World War II for use in radar equipment. At that time E. U. Condon suggested that such short wave lengths might be applied to medicine. This tube oscillates at a high frequency (3×10^9 cycles per second) and has a large output (65 to 80 watts). The short-wave-length energy is focused on the body surface by means of a parabolic reflector. Although tissue penetration of such short waves is less than that of conventional diathermy, the heating of superficial tissues is good.

Discussion

In addition to the devices presented, a host of "ancillary" electronic devices are used in medicine. A few examples illustrate the wide range of uses — radios for hospital patients, digital computers for large-scale data problems, image amplifiers for x-ray fluoroscopy, closed-circuit television for teaching, mass spectrometers, pocket radio receivers for personal paging of doctors in a hospital, tape recorders for teaching purposes and special count-rate meters for work on isotopes.

Conclusions

Members of the medical profession and electronic engineers have shown increasing interest in the field of medical electronics, with the result that electronic instrumentation has contributed to recent advances in some fields of medicine. Greater application of electronic instrumentation to medical problems will result from teamwork between the engineer and physician.

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MEDICAL INTELLIGENCE

TROPICAL EOSINOPHILIA*

Report of Two Cases Occurring More than a Year after Departure from India

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TROPICAL eosinophilia is a syndrome common in India and other tropical areas, variably characterized in the acute stage by fever, malaise, night cough, wheezing respirations and pulmonary infiltration on x-ray examination and in the chronic stage by weight loss, fatigue and the same respiratory symptoms. Eosinophilia is consistently present, and arsenotherapy is specific.[1] The syndrome may develop after the patient has left the tropics; only a few such cases are reported in the American and British literature, and this communication adds 2 more.[2,3] With the movement of sizable numbers of people between the United States and tropical countries now common, this aspect of tropical eosinophilia may become more important in the United States.

The classification of tropical eosinophilia and other syndromes of pulmonary infiltration and eosinophilia is obscure. The existence of several good reviews makes it superfluous to survey the literature here.[4-7] It is worth noting, however, that the ability to relieve the symptoms of tropical eosinophilia (and perhaps of similar syndromes originating outside the tropics[8]) by arsenotherapy makes it important to regard it as a separate entity until it is proved otherwise. Furthermore, as Treu[9] commented in 1944, eosinophilia and the response to arsenotherapy are the only consistent marks of this syndrome, so that a high index of sus-

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picion while the cause of an eosinophilia is under investigation is important in diagnosis.

Case Reports

Case 1. Bh. was born in India in 1921, went to Canada in 1948 and came to Massachusetts in 1950. He had suffered from "dysentery" treated with emetine in 1943, and gave a history of having had mild wheezing respirations with some upper respiratory infections. Otherwise he was well until June, 1951, when he noted fatigue and the sudden onset of right-lower-quadrant pain. He was afebrile and had no respiratory symptoms and no abnormalities on physical examination, except that 1 observer considered the edge of the liver slightly tender. Cephalin flocculation was ++++ in 48 hours. Three stools were negative for ova and parasites, and a film of the chest showed a nonspecific increase in the bronchovascular markings. The serum van den Bergh and the prothrombin time were normal. A marked eosinophilia was present (Table 1). The symptoms subsided without treatment.

Table 1. *Pertinent Data in 2 Cases of Eosinophilia.*

Date	White-Cell Count	Eosinophils %	Remarks
Case 1:			
June 12, 1951	19,100	51	Onset of symptoms; no previous count.
July 12, 1951	12,100	66	Pain gone; fatigue present.
Dec. 12, 1951	14,800	56	Patient asymptomatic
July 10, 1952	14,100	63	Fatigue
Sept. 2, 1952	14,600	71	Patient asymptomatic
Dec. 29, 1953	13,500	52	Onset of asthma
Jan. 15, 1954	9,300	48	After 1 dose of oxophenarsine
Jan. 28, 1954	7,100	34	Oxophenarsine course completed
Aug. 2, 1954	7,000	19	Patient asymptomatic
Sept. 2, 1954	6,200	12	Patient remains asymptomatic
Case 2:			
Feb. 6, 1953	13,300	4	Common cold
Nov. 9, 1953	10,900	50	Onset of symptoms
May 19, 1954	11,900	38	———
June 28, 1954	10,400	43	Before treatment
July 16, 1954	7,200	32	After 4 injections of oxophenarsine
Aug. 24, 1954	6,500	9	Treatment completed
Sept. 22, 1954	9,200	7	Patient asymptomatic

After recurrence of fatigue in July, 1952, a biopsy of the gastrocnemius muscle showed no abnormalities, and an uncertain amount of ACTH was given by another physician. Once again the patient felt better, although the eosinophilia persisted. During May, 1953, he suffered from vague epigastric or right-upper-quadrant distress, which disappeared spontaneously.

On December 27 he first noted wheezing and a dry cough at night. On physical examination there were wheezes throughout the chest, and a lymph node, 1 cm. in size, was found in the right axilla. Another film of the chest showed a questionable nodularity throughout the lung fields. Tedral relieved the symptoms. A consultant immediately suggested the diagnosis of tropical eosinophilia and treatment with arsenic, and 325 mg. of oxophenarsine hydrochloride was therefore given intravenously in 5 doses over 3 weeks. The asthma disappeared after the 2d dose, and the eosinophilia diminished (Table 1). When last seen in September, 1954, the patient had continued to feel entirely well. It seems likely that additional arsenic therapy would have caused the eosinophilia to subside even further, but this seemed an unnecessary measure in view of the symptomatic good health.

Case 2. Da. was born in 1934 and came to Massachusetts from India in September, 1952. In February, 1953, he was in the college infirmary because of an upper respiratory infection. A film of the chest and white-cell and differential counts were normal. He then felt well until November, when he spent 5 days in the infirmary because of headache and fever. There were no localized symptoms, and on physical examination the only abnormalities were a maximum temperature of 101°F. for the 1st 36 hours and considerable generalized adenopathy, which had not been present before. No film of the chest was taken, but the blood showed marked eosinophilia (Table 1). During the winter the patient did poorly because of fatigue, anorexia and a 19-pound weight loss. He noted occasional mild right-lower-quadrant discomfort and reported to the clinic once for a night cough. In retrospect he later thought that he had noted wheezing respirations for a short period.

Because of a noticeable drop in academic performance, he was called to the Medical Department in June, 1954, for review of his health. His complaints were intermittent cough, fatigue and lack of his usual energy; the only abnormal physical finding was generalized adenopathy. The eosinophilia was still present, and a film of the chest was normal. Actually, he felt slightly better than during the winter and had regained about 9 pounds. Tropical eosinophilia was suspected because of the experience with the previous case. Therefore, 430 mg. of oxophenarsine hydrochloride was administered intravenously in 9 doses over 5 weeks. The eosinophilia subsided rapidly, and he reported himself as feeling much better. The cough disappeared, and he regained all the weight he had lost, and recovered his usual zest and stamina. When last seen in November he still felt well, and the adenopathy had regressed partially but not completely.

Summary

Two cases of tropical eosinophilia are reported. They have several common features deserving attention: the appearance of the illness thirty-four and fourteen months after departure from the tropics, the mild nature and late appearance of the respiratory symptoms, the absence of abnormalities of the chest on x-ray examination, the chronic course with vague symptomatology, the occurrence of mild abdominal pain and, most important, the rapid response of the eosinophilia and symptoms to injections of oxophenarsine hydrochloride.

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DOCTORS AFIELD

Rudolf Virchow

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ON the night of March 18, 1848, a young man burst into the office of Dr. Schleich, a physician of Berlin, asking:

> "Schleich, have you any weapons?"
> "Only this old gun and a rusty sabre."
> "Out with them! Off to the barricade!"[1]

Thus, Rudolf Virchow, twenty-seven years of age, rushed off to build barricades and to oppose, with only a pistol, the soldiers of a king. The short range of his weapon limited his effectiveness, since, as he regretfully wrote to his father, "The soldiers shot mostly from too great a distance. . ."

Only three years later the young revolutionary postulated that the primary units of life are the individual cells of the animal body. This doctrine of "cellular pathology" has dominated biology and medicine to the present day. If young Virchow had not gained prominence in medical circles with his famous *Archives,* already in publication before his participation in the 1848 revolution, he might have had to share the fate of many other talented men of the period and flee the country. What would have been the history of pathology in the United States if Virchow had migrated to this country with another "forty-eighter," Carl Schurz? Or, indeed, what would have been the course of world medical history if a rifle ball had penetrated the barricade on March 18, 1848, and cut down young Virchow, much as Massachusetts's own beloved Joseph Warren was lost at Bunker Hill?[2] Fortunately for mankind Virchow lived a long and busy life of eighty-one years, amply fulfilling the title of his composition on finishing gymnasium: "A life full of work and toil is not a burden but a benediction." At death his native land judged him to be her pre-eminent pathologist, anthropologist and sanitarian and her leading liberal statesman. The present account is mostly devoted to Virchow's contributions as a statesman. These and his other activities have been described in detail elsewhere.[1,3-5]

Virchow was the son of a Pomeranian farmer, brought up under the reactionary theories of Metternich and the iron rule of Frederick William III of Prussia. The heel of the *Junkers* was heavy on the small farmers of Prussia, and Virchow reacted by fighting this political oligarchy for the rest of his career. His opportunity to study medicine came when he was accepted at the Friedrich-Wilhelms Institut in Berlin. This institute provided free medical education to a certain number of students in return for later employment as army doctors. Such a contract of indenture did not deter Virchow from enrolling in 1839 or from graduating in 1843. He came under the influence of the great embryologist Johannes Mueller during his medical schooling, and his lifelong interests appear to have been conditioned by that teacher. After graduation he became a military "company surgeon," but this did not seem to stand in the way of experimental work. In spite of his youth, he rapidly rose to a position of prominence in Berlin medical circles. During the winter of 1847-1848 he was sent by the Government to survey the medical situation in Upper Silesia, where a typhus epidemic was devastating a half-starved population. This survey apparently prompted his opinions about the inability of the German monarchy to provide adequately for the people. He delivered a stinging report, laying the epidemic's causative factors at the door of the Government. His suggested therapy for the situation was "full and unlimited democracy." Virchow made specific proposals designed to raise the public welfare and thus to head off such epidemics amongst the poverty-stricken, uneducated population of Upper Silesia. This was strong medicine for the Hohenzollerns, and Virchow was not to hear the last of it.

Virchow during His Professorship at Würzburg, 1849-1856 (Courtesy of the Syracuse University Library — Print No. 5571 in the Wolff–Leavenworth Collection).

Meanwhile the revolution of 1848 took place, shortly after Virchow's Silesian survey. This brief democratic victory resulted in his actually being elected into the Prussian Diet, but he was too young to take office. After a few months of indecision the forces of the

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monarchy began to rally. Virchow did not slacken his intense activity in democratic meetings and clubs, nor did other courageous physicians such as Ignaz Semmelweis, Ludwig Traube and Robert Remak. Virchow expressed his personal indebtedness to his superiors on the faculty, who apparently experienced difficulties because of his political activities, but he made it clear that this could not compromise his opposition to the principles of the reigning monarchy. He deeply admired the political structure of the United States, and wanted a German republic based on the premises of equal rights for all citizens and a maximum of self government, principles reminiscent of the earlier handiwork of Thomas Jefferson in our country. With uncanny prescience Virchow stated, "Either Germany becomes a republic, or it ceases to exist and becomes Russian."[1] He had no faith in attempting to incorporate the Hohenzollerns into a constitutional monarchy similar to the government of England. He believed that this particular ruling family under any arrangement would be paternalistic and authoritarian toward the people, no matter what a constitution might say. It is not surprising that by the spring of 1849 he was suspended from his job. There were immediate protests from his students and from medical circles, with the result that he was reinstated "on probation," but with a reduction in effective income.

In spite of this political turmoil, Virchow was soon called to Würzburg as the occupant of the first chair of pathological anatomy in Germany. For seven fruitful years he labored there, and the pupils he and his colleagues attracted soon gave this university international fame. During these years he entered little into political activity, finding compensation in scientific productivity. It was here in 1855 that the terms "cellular pathology" and *"omnis cellula e cellula"* were first given to the medical world in his *Archives.* Not satisfied with initiating one journal, he took part in launching two other publications, a yearbook later known as *Virchows Jahresbericht* and a handbook of special pathology and therapeutics that was the first example of the famed German medical handbooks.

In 1856 he accepted the chair of pathological anatomy in Berlin, the city from which he had been driven seven years earlier. There he began a period of forty-six years of intensive work, training later leaders such as Hoppe-Seyler, Salkowski, Von Recklinghausen, Cohnheim, E. Klebs and Reginald Fitz.

In 1861 King Frederick William IV died and was replaced by his brother, William I. As a result of changes in governmental policy, possibly on the basis of sibling rivalry, many of the "forty-eighters" reentered political life. Included among them was Virchow, who was elected to the Berlin city council in 1859. In the same year he took part in the founding of the *Deutscher National-Verein,* a political group favoring unification of Germany, and was influential in the formation of the German Progressive Party in 1861. In December, 1861, he was elected to the lower house as a member of that party.

The new king, a former general, was much interested in strengthening the *Junker* army. For this he needed an increased budget, and this was opposed by Virchow's party. As a leader in the opposition party at this time Virchow achieved his political prominence, since this very budget crisis resulted in the appointment of Otto von Bismarck as prime minister. Bismarck promptly violated the 1848 constitution by dissolving the parliament with the antidemocratic announcement: "The great questions of the time will be decided, not by speeches and resolutions of majorities . . . but by iron and blood."[1] This ominous pattern of thought was voiced again and again as Germany played out her political tragedy.

At the start of the next parliamentary session (1863) Virchow presented an appeal to the King to put an end to such breaches of the constitution, but to no avail. This was the beginning of a long political battle between Bismarck and Virchow. By 1865 Bismarck had become so irritated with his scholarly antagonist that he challenged Virchow to a duel (Bismarck was a well trained duelist). Virchow wisely declined the opportunity and continued his opposition to the absolutism of Bismarck. To do so was not without possible hazards, since Bismarck systematically intimidated those who dared oppose him. This he did by subjecting them to repeated subpoenas for their remarks, and even by jail terms.

As the time for the Franco-Prussian war approached, Virchow's party progressively lost ground. In 1869 Virchow warned against new wars, remarking that there had been more than enough blood and iron on the road to German unity. The inevitable conflict took place in 1870 with France, during which Virchow devoted himself entirely to medical work. Virchow's political influence declined markedly in the 1870's as the result of a temporary *mariage de convenance* that he unwisely made with Bismarck during the Chancellor's excursion into the field of church-state relations.

A young Canadian physician named William Osler spent a short time with Virchow during this period. Years later Osler, then professor of medicine at Johns Hopkins University, delivered a moving address on the occasion of Virchow's seventieth birthday.[3] It is of considerable interest that much of Osler's discourse was devoted to Virchow the humanist, rather than to the technical aspects of Virchow's medical achievements, as the following passage indicates:

> The conditions in Germany have not been favorable to a man of advanced liberal views, and Virchow has been attached to a party which has not been conspicuously successful; but he has been an honest and industrious worker, a supporter of all measures for the relief of the people, a strenuous opponent of all class and repressive legislation, and above all an implacable enemy of absolutism as personified in Bismarck . . .
>
> As an illustration of his capacity for varied work, I re-

call one day in 1884, in which he gave the morning demonstration and lecture at the Pathological Institute, addressed the Town Council at great length on the extension of the canalization scheme, and made a Budget speech in the House, both of which were reported at great length in the papers of the next day.[5]

Virchow's civic tasks were made easier by the fact that his old friend, Dr. Paul Langerhans, Sr., was president of the city council; Langerhans had helped Virchow found the German Progressive Party in 1861, and was father of the histologist who immortalized the family name.

Virchow sat in the *Reichstag* until 1893 and in the *Landtag* until after the turn of the century. He was made rector of the University of Berlin in 1893 at the age of seventy-one. In 1902 he broke a femur alighting from a streetcar in Berlin and died from the complications of this injury.

Virchow was possibly the nineteenth century's best example of the "whole man," straight out of the Renaissance. Although his political contributions are not widely appreciated, his full stature in that field may not yet have been reached. Of this, Ackerknecht[1] observes:

> The story of Virchow's political life is essentially a story of courage, insight, and devoted industry. And yet it came to nought — primarily not through the errors of the hero, considerable as they were sometimes, but through his being chained to a class and a nation involved in insoluble contradictions and paralyzed by traditions of submission. It is easy to see how different Virchow's political career would have been had he lived in France, England or the United States . . .
>
> It seems quite possible that — once the Germans have fully realized the consequences of Bismarck's victory and the Western world has reached a full understanding of the impact of the miscarriage of German democracy on its own fate — posterity might . . . respect Virchow for his consistent opposition to Bismarck in a decisive moment of history as deeply as it now respects him for his scientific achievements.[1]

For source material I am heavily indebted to Ackerknecht's[1] biography of Virchow. Mr. L. G. Wells, curator of Special Collections at the Syracuse University Library, provided valuable assistance.

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Bookplate Collection of the Boston Medical Library

3. Bookplate of Oliver Wendell Holmes (1809-1894), charter member and first president of the Library (1875-1888). In 1889 he presented to the Library his valuable collection of 1000 volumes, rich in books on anatomy, plate books and medical classics. The bookplate depicts the Nautilus shell, the inspiration of one of his best loved poems, *"The Chambered Nautilus,"* first published in the *Autocrat of the Breakfast Table* (Boston, 1858). A polished shell from the library of Dr. Holmes is in the Holmes collection in the library.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41141

PRESENTATION OF CASE

First admission. A sixty-nine-year-old retired clothes presser was admitted to the hospital because of a stiff neck.

Five days before admission, after mowing the lawn, the patient felt weak and noted a stiff neck. Two days later his son, a physician, examined him and observed no positive findings. On the evening of admission the neck became more painful, the temperature was 102.2°F., and he was sent to the emergency ward.

He had had heart trouble and high blood pressure for over thirty years and was said to have stopped working because of it. Five and a half years before admission a cataract had been removed from the left eye. At that time the blood pressure was 210 systolic, 110 diastolic, and the pulse 80; the apex of the heart was 1 cm. to the right of the midclavicular line, and the aortic second sound was louder than the pulmonic. After severe trauma in an automobile accident four years before admission, he was said to have had no hypertension. He was alleged to have had a stroke ten or twelve years before admission, with aphasia and paralysis, but whether of the right or left side was unknown. He had had episodes of squeezing chest pain without radiation and dyspnea on exertion and had been under a physician's care for heart disease but had taken no medication.

Physical examination revealed a moderately obese man, groaning and sweating. The tongue deviated to the left. The neck was tender to palpation and rigid and could not be moved in any direction. No cervical lymph nodes were felt. Inspiratory and expiratory fine, moist rales were heard at both bases, and expiratory wheezes over the anterior part of the chest. The heart was enlarged, with a Grade 2 to 3 systolic murmur heard in all areas and described by one observer as loudest in the pulmonic area and by another as transmitted to the neck. The neck veins were distended. The fingers were clubbed, and the nails cyanotic. There was tenderness over the lateral aspect of the left tibial tuberosity. The left calf was tender and larger in diameter than the right. No dorsalis-pedis or posterior-tibial pulses were felt. There was some weakness in the left quadriceps muscle. The deep tendon reflexes were normal. The Kernig sign was negative; the plantar reflexes were flexor, and no sensory deficit was present.

The temperature was 100.2°F., the pulse 116, and the respirations 36. The blood pressure was 134 systolic, 88 diastolic.

The urine had a specific gravity of 1.032 and gave a + test for albumin, and the sediment contained rare red cells and white cells and casts. Examination of the blood revealed a white-cell count of 13,800, with 87 per cent neutrophils, and a hemoglobin of 14.8 gm. per 100 cc. The prothrombin time was 12 seconds (normal, 13 seconds). Lumbar puncture showed that the cerebrospinal fluid was under an initial pressure equivalent to 180 mm. of water and that the dynamics were normal. Twelve red cells and 1 white cell per cubic millimeter were seen in the spinal fluid; the protein was 62 mg. per 100 cc.; the Hinton test was negative, and the culture showed no growth. One stool gave a ++ guaiac reaction, and another was guaiac negative. An electrocardiogram demonstrated a normal sinus rhythm, right-bundle-branch block and occasional ectopic ventricular premature beats; the T waves were upright in Leads 1, aVL and V_2 through V_6, and the ST segments depressed in Leads V_4 through V_6 and inverted in Leads 2, 3, and aVF; the Q waves were prominent in Leads 2, and aVF, and RR′ waves were present in Leads V_1 and V_2. There was no change from a tracing done three years previously.

An anteroposterior film of the chest taken in the supine position showed a considerable increase in pulmonary vascular markings at both hilar areas and peripherally. In the right-upper-lung field the pulmonary densities appeared more patchy in distribution. The heart was enlarged, principally in the region of the left ventricle, and the cardiothoracic ratio was 17.5:31.5. The aorta was tortuous and calcified. Films of the cervical spine showed marked degenerative changes at the level of the fifth and sixth cervical vertebras. The vertebras below the fifth cervical level were not adequately seen in the lateral view. No bone destruction was recognized.

In the hospital the patient was treated with digitoxin, analgesics and a Thomas collar. After three days, the lungs were clear to auscultation, and the neck veins were no longer engorged, but the neck was still very stiff and painful. On the fourth day, digitoxin was stopped because of ventricular premature beats. A second electrocardiogram showed no significant change from the previous one, with no evidence

of digitalis intoxication, so digitoxin was resumed after three days. The neck pain diminished somewhat toward the end of the hospital stay. The temperature, which had been 102 and 101°F. on the first and second days, subsequently ranged between 99 and 100°F. by rectum. He was discharged on the tenth hospital day on a maintenance dose of digitoxin, a diet with no added salt, a collar for his neck and aspirin.

Final admission (twelve days later). Since discharge he had not been well and had refused food and drink. The neck pain, although less severe, persisted. Four days before admission he was noted by his physician son to have Cheyne–Stokes respiration. He was cyanotic, and the systolic blood pressure was 80 to 90. He had a shaking chill, with a temperature of 103.4°F., which dropped to normal in twelve hours. Oral administration of penicillin, 800,000 units a day, was begun. The temperature had not risen again.

On admission he was dehydrated, critically ill and unresponsive. The neck was very stiff and painful to the slightest movement. Respiration was of Cheyne–Stokes type. The lungs were clear. The neck veins were not distended, and the heart was not enlarged. A Grade 2, rough systolic murmur was heard at the left sternal border. The aortic second sound equaled the pulmonic. One observer found that the left biceps and triceps reflexes were absent; the plantar reflexes were flexor. The patient was hiccuping and complained of pain on palpation or percussion of any area of his body.

The temperature was 100°F., the pulse 60, and the blood pressure 90 systolic, 65 diastolic.

The urine had a specific gravity of 1.008, and the sediment contained occasional cells. Examination of the blood revealed a white-cell count of 8900, with 89 per cent neutrophils, many of them band forms, and a hemoglobin of 13.6 gm. per 100 cc. The blood sodium was 132 milliequiv., the chloride 87 milliequiv., and the carbon dioxide 30 milliequiv. per liter; the nonprotein nitrogen was 50 mg. per 100 cc. After two days the chloride had risen to 103 milliequiv., and the potassium was 4.7 milliequiv. per liter. A lumbar puncture on the third day showed that the cerebrospinal fluid was under an initial pressure equivalent to 75 mm. and a closing pressure equivalent to 40 mm. of water, but because of a leaking valve the pressures may have been incorrect. Dynamics were normal. The fluid was clear and colorless and contained no white cells and 267 red cells per cubic millimeter. The total protein was 54 mg., and the sugar 104 mg. per 100 cc., the chloride 108 milliequiv. per liter, and the colloidal-gold curve 0011111000. X-ray films of the chest showed at least as much pulmonary vascular congestion as on the previous admission (and probably more), but respiratory motion obscured fine detail. At this time the films from the first admission were reviewed, and miliary densities were noted. These were thought also to be present on the last films, but motion obscured them.

The patient continued to be very ill and was sometimes more and sometimes less responsive. The spleen became palpable on the third hospital day. He was given digitoxin and 300,000 units of crysticillin twice daily, as well as intravenous injections of fluids since he refused to drink. On the fifth hospital day he was found sweating and minimally cyanotic. The respirations were regular at a rate of 40, with a prolonged expiratory phase, and musical rales could be heard without a stethoscope. He was given 0.5 gm. of aminophylline over a period of two or three minutes during which the pulse was checked and found to be steady. About a minute later he died.

In the hospital he had a minimum temperature of 99°F. by rectum but never higher than 101°F. and blood pressures of 90 to 100 systolic, 50 to 60 diastolic. After the second hospital day the pulse gradually rose from 60 to 90 at the time of death.

Differential Diagnosis

Dr. Walter Bauer*: Was the spleen larger during the second admission than it had been previously?

Dr. John W. Keller: Yes; it was.

Dr. Bauer: Can you tell me anything about the neck veins during the last episode?

Dr. Keller: They were distended.

Dr. Bauer: Was there any pain at that time?

Dr. Keller: He complained of pain wherever one touched him.

Dr. Bauer: Did he have substernal pain?

Dr. Keller: I am sure he did not complain of substernal pain, but he was a difficult patient to assess.

Dr. Bauer: Had he had pain before the final illness?

Dr. Keller: Before the stiffness of the neck, he had no pain. The neck pain persisted throughout the illness.

Dr. Bauer: When one is confronted with referred pain of the type that this man had, central-nervous-system disease, osseous disease and articular disease first come to mind. There is little in the clinical record favoring the presence of any of these diseases. Was there any suggestion of a soft-tissue mass in the cervical region? I assume that there was not. Can we rule out a tuberculous granuloma of the bone?

Dr. Joseph Hanelin: The films of the neck show only questionable bone destruction in the lower cervical region. I do not see any paravertebral soft-tissue thickening. The first films of the chest demonstrate enlargement of the heart, with evidence of congestive changes in both lungs. In addition there are a few scattered densities, which may or may not be vascular in character, but do raise the possibility of a miliary parenchymal process over and above the congestive change.

Dr. Bauer: Was there a pleural effusion?

Dr. Hanelin: There is no evidence of any effusion on the last film, taken about three weeks later, and no particular change in the status of the heart or lungs.

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DR. BAUER: What are these small shadows in the lungs?

DR. HANELIN: For the most part they appear to represent dilated small vessels. The abdominal films, taken at the last admission, give evidence of splenic enlargement.

DR. BAUER: Was the urine abnormal on the second examination?

DR. KELLER: No; it was normal.

DR. BAUER: There can be little doubt that this man had arteriosclerotic and hypertensive heart disease and atherosclerosis of the aorta. He was known to have had hypertension thirty years previously. Though the blood pressures had reverted to normal within the last five years there was probably evidence of the inroads of hypertension. Is that true, Dr. Palmer?

DR. ROBERT S. PALMER: Yes.

DR. BAUER: He had been treated for "squeezing chest pain" without radiation and for dyspnea on exertion. Though he had been under a doctor's care no medication was taken. This suggests the possibility of a hiatus hernia, as well as coronary-artery disease. I do not wish to make too much of this because the other clinical findings are more important.

Is more detailed information concerning the examination of the neck available? Was there any point tenderness or limitation of lateral, forward or backward motion?

DR. PALMER: He could not lift his head, and his neck remained rigid when his head was lifted for him. I did not specifically try lateral motions.

DR. BAUER: Information of this type is necessary for the diagnosis of meningeal disease or disease of the bony or articular structures.

I do not know how to interpret the tenderness over the left tibial tuberosity. Osgood–Schlatter disease does not occur at this age. Lesions in this area are very rarely due to metastatic carcinoma.

It appears that the patient had phlebitis. He also had severe arteriosclerosis of the arteries of the legs, as indicated by the absence of the dorsalis-pedis and posterior-tibial pulses. Yet there was no history of intermittent claudication on walking. He did have weakness of the left quadriceps-muscle group. It seems unlikely that this was a residuum from the "stroke" because the tongue deviated to the left. The laboratory tests were not remarkable. I do not attach any significance to the 12 red cells in the cerebrospinal fluid. I agree with the radiologist that the changes noted in the x-ray films of the lungs were the result of pulmonary edema and not an infectious disease. The x-ray films showed marked degenerative joint disease of the cervical spine most evident in the fifth cervical vertebra. Such changes are frequently seen though they rarely cause symptoms of the type described.

After discharge he continued to have "neck" pain. Though he showed no signs of heart failure his family physician noted the systolic pressure was 80 to 90 as opposed to the hospital reading of 138. The lowered pressure strongly suggests myocardial infarction. Subsequently, he had a shaking chill, with a temperature of 103.4°F., for which he was given penicillin, 800,000 units a day by mouth.

When readmitted to the hospital he was critically ill, but there were no signs of congestive heart failure. Again, there was some question about the reflexes. One examiner reported absence of the left biceps and triceps reflexes.

DR. EDWARD P. RICHARDSON, JR.: I saw the patient briefly when he was in a terminal state; then examination of the reflexes was unsatisfactory.

DR. BENJAMIN CASTLEMAN: Dr. Charles S. Kubik saw this patient during the second admission and said in a note: "Arm jerk, knee jerk and ankle jerk, faint or not obtained, but here again examination is most unsatisfactory; the same thing is true of plantar reflexes and sensation, although pinprick and tactile stimuli are obviously felt everywhere."

DR. BAUER: If these reflexes were absent there must have been a pathologic process involving the fifth, sixth and seventh cervical nerves. To account for their absence on the basis of degenerative joint disease one must postulate the presence of spurs compressing either the spinal cord or the nerve roots. This would be most unlikely. Nor do I believe that intrinsic disease of the nervous system was present because of the paucity of neurologic abnormalities.

There is a statement that the patient was tender no matter where he was pressed. Does this mean soft tissue as well as bone?

DR. KELLER: Yes.

DR. BAUER: That does not help. If it had been bone pain, one would have to entertain the possibility of multiple myeloma.

The enlarged spleen, the chills and the question of miliary lesions in the lungs suggest the presence of infection. With no pus in the urine on the second admission and a nonprotein nitrogen of only 50 mg. per 100 cc. I cannot make a diagnosis of pyelonephritis and thus explain the palpable spleen. I should like to think it had been enlarged for years. The elevated nonprotein nitrogen probably reflects arteriosclerotic renal disease.

My problem is to decide what caused the painful neck. The only neurologic abnormality that points to disease in the central nervous system is the slight elevation of spinal-fluid protein; however, that would not be an unusual finding in a man of sixty-nine without demonstrable central-nervous-system disease. Is that not true, Dr. Richardson?

DR. RICHARDSON: It is true that it may not be of any serious importance.

DR. BAUER: I shall assume that the biceps and triceps reflexes were absent. Yet there is no evidence of a lesion in the central nervous system other than the old cerebral accident. Nor is there any indication of disease involving bone as judged by the x-ray film of

the cervical spine, the absence of point tenderness and so forth. Rarely, a dissecting aneurysm of the aorta will cause a very painful, stiff neck, but there is nothing to suggest this diagnosis in the case under discussion. The 267 red cells in the cerebrospinal fluid may have been the result of the lumbar puncture. I do not think they are of any diagnostic significance.

Tuberculosis of a vertebra, with or without a cold abscess, as a manifestation of miliary tuberculosis cannot be diagnosed from the data at hand. A staphylococcal septicemia could account for this clinical picture; however, the pulmonary lesions are usually bilateral and go on to abscess formation. There may be associated cortical abscesses of the kidneys and foci of osteomyelitis to which the cervical spine is certainly not immune. Though there was no evidence of meningitis, there need not be until the focus of osteomyelitis gains access to the dura. Once this takes place the meningitis may be severe and fatal. I cannot make a diagnosis of staphylococcal septicemia on the basis of this clinical record.

The one condition that would best account for absent biceps and triceps reflexes and the stiff painful neck is a ruptured disk. The slight elevation of spinal-fluid protein would be in keeping with this diagnosis. In making this diagnosis I realize that I am on thin ice and have left many things unaccounted for.

Why did the patient die? Why was he so unresponsive? Why did the spleen become palpable? I first thought the palpable spleen was secondary to a pyelonephritis. This not being present, I am left without a cause for the splenomegaly. Did he have cardiac asthma? Is that why he received the aminophylline? I shall assume that he died of cardiac standstill secondary to coronary-artery disease and not of a dissecting aneurysm with cardiac tamponade.

My final diagnoses are coronary-artery and hypertensive heart disease, extensive atherosclerosis of the aorta, nephrosclerosis and a ruptured intervertebral disk. He may have had a bacteremia to account for the chills, fever and splenomegaly. If so, I do not know its origin or the causative organism. In making these diagnoses I am disregarding the splenomegaly. In doing so I must assume that it had been present for a long time. It may have been due to past malaria. I must admit that I am not too happy with this explanation. I keep wishing I could tie it all together more satisfactorily, but somehow I seem to have failed.

A PHYSICIAN: Would you consider a polyarteritis?

DR. BAUER: I thought of it, but there was little to favor it. Why did you consider it?

A PHYSICIAN: Neck tenderness, leg tenderness and the lesions in the lungs.

DR. BAUER: The patient had hypotension instead of hypertension.

A PHYSICIAN: He had had hypertension up to four years before admission.

DR. BAUER: Yes, but there is not much to support the diagnosis; there was no leukocytosis, no eosinophilia and no skin manifestation. Although he was sensitive all over the body, there was no evidence of peripheral neuritis.

DR. LEWIS W. KANE: Would you consider subacute bacterial endocarditis in view of the fever and the clubbed fingers?

DR. BAUER: Did he have clubbed fingers? I failed to note that.

DR. KANE: The clubbed fingers, the fever and the palpable spleen and also the bizarre symptoms could be explained by subacute bacterial endocarditis.

DR. BAUER: The diagnosis of subacute bacterial endocarditis is an excellent suggestion. I missed the fact that he had clubbed fingers although I read the protocol two or three times. Where would you place the focus?

DR. KANE: The aortic valve.

DR. BAUER: Endocarditis in a man sixty-nine years of age may well be of the type seen in elderly patients. It is well known that positive blood cultures in elderly patients dying from tuberculosis, cancer and other long-lasting emaciating diseases are obtained. In some of these cases platelets are deposited on the valves, where the bacteria then settle, and an acute endocarditis results.

DR. JACOB C. LERMAN: The patient may have had long-standing bronchiectasis and may have acquired a metastatic infection such as an epidural abscess.

DR. BAUER: An epidural abscess would have caused abnormal spinal-fluid findings. I do not believe he had disease of the central nervous system other than that caused by the "shock" eleven years before admission.

DR. CASTLEMAN: Dr. Palmer, what did you think the patient had before he died?

DR. PALMER: I thought of epidural abscess; so did Dr. Kubik when he first saw the patient. The neck was very painful, but we did not think of waggling it from side to side. Also, the murmur at the apex grew progressively more marked over a three-year period, and he was thought to have progressive sclerotic or calcific valvular disease.

DR. BAUER: Were blood cultures done?

DR. KELLER: No.

CLINICAL DIAGNOSES

Metastatic carcinoma to lung and ?to cervical spine (primary site unknown).
Arteriosclerotic heart disease, with congestive heart failure.

DR. WALTER BAUER'S DIAGNOSES

Coronary-artery disease.
Hypertensive heart disease.
Extensive atherosclerosis of aorta.
Nephrosclerosis.
Ruptured intervertebral disk.

Anatomical Diagnoses

Subacute bacterial endocarditis, superimposed on calcareous aortic stenosis.
Chronic osteomyelitis, sixth dorsal vertebra.
Clubbed fingers.
Cardiac hypertrophy.
Coronary-artery disease, with old thrombosis and infarction.
Cerebral infarct.
Hydrothorax, bilateral.

Pathological Discussion

Dr. Castleman: At autopsy there was about a half a liter of fluid in each pleural cavity. The heart was enlarged, weighing 520 gm.; most of the enlargement was of the left ventricle. We found an old occlusion in the right coronary artery and corresponding to that a fairly large old myocardial infarct. I think that this myocardial infarction may have brought down the blood pressure. We found in the brain evidence of the old "stroke" — a marked softening — and also evidence of the cerebral accident four years previously: several brown-stained (hemosiderin) depressions such as one sees with trauma.

The aortic valve showed extensive calcareous deposits. One of the cusps was covered with vegetations and perforated — findings characteristic of a bacterial endocarditis. On microscopical examination the vegetations had an amorphous appearance and showed a tremendous amount of polymorphonuclear infiltration. In the circumflex branch of the left coronary artery was an embolus of the same material so that the occlusion must have occurred between the two admissions because the infarct of the myocardium that it had caused was very recent — marked infiltration with polymorphonuclear leukocytes.

The sixth cervical vertebra was soft. When the dura close to this vertebra was opened there was a hemorrhagic discoloration — enough to give about 200 cells in the fluid. There was no pus. The section of the vertebra showed a healing process — a great deal of young connective tissue and considerable vascularity but no polymorphonuclear leukocytes. This chronic process extended into the intervertebral disk between the fifth and sixth vertebras. I believe the lesion was chronic osteomyelitis, and since the first symptoms appeared in the neck it may have been the focus, which produced the subacute bacterial endocarditis.

The spleen weighed 500 gm. and showed chronic inflammation. We found nothing remarkable in the kidneys. We looked very carefully for any evidence of embolic nephritis.

Dr. Bauer: Was there any nephrosclerosis?

Dr. Castleman: Yes; but it was minimal.

Dr. Bauer: I think it is of interest that I read this case record at least twice and on no occasion did I note that the patient had clubbed fingers. If I had noted them I might have paid more attention to the systolic murmur.

CASE 41142

Presentation of Case

First admission. A thirty-nine-year-old nurse was admitted to the hospital because of abdominal soreness and for diagnostic study of palpable abdominal masses.

Nine months previously, when she was given a routine pre-employment physical examination, she was in good health. The heart and lungs were normal. On abdominal examination, however, several discrete, hard, freely movable, "orange-sized" nodules were both visible and palpable throughout the right side of the abdomen and both flanks. These masses descended with respiration; the outline of organs could not be determined because of the masses. There was a mild diastasis recti and a small midline hernia just inferior to the umbilicus. No pelvic masses were felt. The rectal examination was negative. The blood pressure was 150 systolic, 100 diastolic. The urine had a specific gravity of 1.020, gave a + test for albumin and was otherwise negative. The hemoglobin was 13 gm. per 100 cc.; the white-cell count was 8700, with a normal differential, and the erythrocyte sedimentation rate 18 mm. per hour. An x-ray film of the chest showed clear lung fields and a prominent left ventricle. A barium-enema examination outlined a normal colon and distal ileum. The liver was enormously enlarged and extended 2 fingerbreadths below the iliac crest. The splenic shadow could not be demonstrated. The shadow of the right kidney was not seen; that of the left was visualized in the upper outer portion and appeared normal. A barium meal outlined a normal esophagus (Fig. 1); there was a suggestion of extrinsic pressure in the region of the pylorus. The remainder of the small intestine was normal. The patient refused hospitalization and returned to work. During the ensuing four months she continued in good health, but at a follow-up visit she complained of constipation, epigastric fullness and easy fatigability. Her friends thought her color had become more sallow and her abdomen enlarged, but she could not be certain of this, nor could she be certain of any weight loss. She now agreed to enter the hospital.

"Years ago" she had been told that she had a cyst on the right kidney, but had never had genitourinary symptoms. Her mother had died of polycystic kidneys.

Investigation revealed a normal prothrombin time, nonprotein nitrogen, alkaline phosphatase, total serum protein and albumin-globulin ratio. Peritoneoscopy showed large, thin-walled cysts in the liver and possibly in the omentum and bowel. An intravenous pyelogram outlined very large, smooth kidneys (Fig.

2). Excretion was markedly delayed on both sides, especially the left. The calxyes on the right were dilated and distorted and had sharp contours; those on the left were elongated and distorted but did not appear dilated. The bladder shadow was normal. The patient was discharged after two days in the hospital.

Second admission (fourteen months later). She was admitted to the emergency ward because of a sudden onset of sharp abdominal pain on the right, radiating around the flank and to the back. The pain came on while she was bending forward getting out of bed. It subsided after a short while, leaving a dull ache in the right side of the abdomen that was almost entirely absent when she was reclining but was quite apparent as a "pull" when she was in the erect position. On examination the abdomen was soft, and there was mild, deep tenderness in the right flank, right lower quadrant and right costovertebral angle. There was no rebound tenderness. The abdominal masses previously noted were readily palpable.

FIGURE 1. *Posteroanterior Film of the Gastrointestinal Examination, Showing Barium in the Stomach and Small and Large Bowel.*

Areas of extrinsic pressure on the stomach and bowel are indicated by arrows. The hepatic flexure of the colon is displaced downward.

The temperature, pulse and respirations were normal. The blood pressure was 180 systolic, 120 diastolic.

The urine gave a trace test for albumin; the sediment contained many epithelial and white cells and 2 to 4 red cells per high-power field. Examination of the blood revealed a hemoglobin of 14.5 gm. per 100 cc. and a white-cell count of 10,750. The nonprotein nitrogen was 34 mg., and the total protein 7.2 gm. per 100 cc., with an albumin-globulin ratio of 2.2. The patient gradually improved on bed rest and was discharged on the fifth day feeling much better, but not well.

Final admission (two months later). She was well and had worked daily. Early on the morning of admission, shortly after rising, headache and dizziness

FIGURE 2. *Intravenous Pyelogram, Showing Greatly Enlarged Kidneys.*

The lateral calyxes are distorted and elongated on the left. There is also calyceal distortion on the right associated with a moderate hydronephrosis.

suddenly developed. This was immediately followed by a tonic seizure lasting several minutes, after which she regained consciousness. She complained of nausea, a stiff neck and headache and had several episodes of vomiting.

Physical examination revealed a pale, noncyanotic woman covered with perspiration. She was oriented, but barely responded to the spoken voice and occasionally uttered irrelevant phrases. The pupils were miotic and responded sluggishly to light. The corneal reflexes were absent. The right eye tended to abduct. The neck was very stiff and resisted forward flexion, though it could be rotated laterally. The lungs were clear to percussion and auscultation. The heart rate was rapid and irregular, and no murmurs were heard. The abdomen was lumpy, as previously described. The extremities could be moved spontaneously. The deep tendon reflexes were hyperactive — more so on the left side. The Babinski reflexes were negative. The abdominal reflexes were absent.

The temperature was 99.2°F., the pulse 150 and irregularly irregular, and the respirations 15 and Cheyne–Stokes in character. The blood pressure was 150 systolic, 90 diastolic.

The urine had a specific gravity of 1.016 and gave a + test for albumin; the sediment contained 15 to 20 red cells and 2 to 4 white cells per high-power field, but no casts. The hemoglobin was 15 gm. per 100 cc., and the white-cell count 11,700, with 90 per cent neutrophils. Lumbar puncture revealed grossly bloody cerebrospinal fluid, with a xanthochromic supernatant fluid under an initial pressure equivalent to 300 mm. and a closing pressure equivalent to 260 mm. of water.

Six hours after the onset coma deepened, and the right arm and leg became flaccid. Nine hours later the blood pressure rose to 220 systolic, 140 diastolic. Cheyne–Stokes respiration was pronounced, with apneic intervals as long as twenty-five seconds. Three hours later the patient had a clonic seizure beginning in the right foot and spreading to the right arm and face that lasted four minutes. She died eighteen hours after the onset.

Differential Diagnosis

Dr. Robert L. Berg*: I think we might start with the x-ray films.

Dr. Joseph Hanelin: Two chest films taken about seven months apart show the same findings — that is, clear lungs and some prominence of the left ventricle.

The barium-enema examination fails to show any intrinsic disease of the large bowel. The hepatic flexure and transverse colon are low in position. There appears to be a considerably enlarged left kidney; the right renal outline is not too well defined, but it is better seen in the pyelogram and is distinctly enlarged. Although I cannot completely trace the liver margin I suspect it is also increased in size. No intrinsic disease was demonstrated in the upper gastrointestinal tract or small bowel. However, there does appear to be some extrinsic pressure on the gastric antrum and widening of the duodenal loop (Fig. 1). The pyelogram more clearly demonstrates the outlines of the greatly enlarged left kidney, whose calyxes are elongated (Fig. 2). There is more marked dilatation of the renal pelvis and calyxes on the right.

Dr. Berg: Would you say that the kidneys are characteristic of polycystic kidneys?

Dr. Hanelin: Yes; they are.

Dr. Berg: Actually, the combination of circumstances in this patient leaves little doubt about the diagnosis. She had a family history of polycystic kidneys, had polycystic kidneys herself, had an episode that apparently was renal colic and finally died in all probability with a ruptured aneurysm in the circle of Willis. The combination of polycystic disease and aneurysm of the circle of Willis is now well enough established as a syndrome to make any other diagnosis difficult. I think the final episode was not only rupture into the ventricles but also considerable bleeding into the left hemisphere, which accounted for the lateralization. On that basis I think that the aneurysm was undoubtedly located at the bifurcation of the left middle cerebral artery. The making of this diagnosis was considerably facilitated by my hearing a case discussed, which I am sure was this one, so it leaves me free to discuss other aspects of the case.

The association of the polycystic disease with aneurysm of the circle of Willis has been known since Dunger[1] described 4 such cases in 1904, but has been missing from the literature until the last two or three years during which there have been a number of articles dealing with the syndrome. Whenever we have a remarkable combination of disorders such as polycystic disease and an aneurysm it is interesting to speculate about what the basic disorder is. Very often, when several congenital disorders coexist, it is considered to be an act of God, or the intervention of bad germ plasm, and something that one cannot pursue further. But in fact the distribution of coexisting congenital lesions is far from random, and results in definite constellations, without doubt. I am sure that, in the long range, medical science will be able to elucidate these syndromes as single basic mechanisms that give rise to anatomically scattered disorders.

In this particular situation it is interesting to recall the disorders associated with aneurysms of the circle of Willis; these include hypertension, frequent coarctation of the aorta and occasional patent ductus arteriosus. Polycystic disease of the kidney is often associated with polycystic disease of the liver and less frequently of the pancreas, lung and spleen. Other conditions noted with polycystic disease are the absence of the gall bladder, primary renal and cerebral neoplasms, glaucoma, myopia, polydactylism and rhabdomyoma of the heart.

The discussion of the mechanisms by which these two congenital disorders may be related can be grouped under three headings: external agents, metabolic abnormalities and congenital malformations. It has been reported in the last two or three years[2] that rats fed sweet-pea seed will develop a disorder, which has been called lathyrism after the biologic name of sweet peas. This condition consists of dissecting aneurysm, inguinal hernia, kyphoscoliosis, epiphysitis and other derangements of cartilaginous growth. In the work on lathyrism one thing is very evident—that the single concept that can pull all the findings together is that there is a toxic compound in the sweet-pea seed, which has been identified as a beta-aminopropionitrile compound[3] that somehow prevents the basic ground substance — the cement substance — from developing properly and thus holding things together correctly. That may be a useful concept if one can find comparable disorders in human beings. In fact I have heard that one study is being done on this subject in another city, the results of which have not yet been published; this study suggests that there is a reasonably good chance that dissecting aneurysms

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are associated with bony disorders in an unexpectedly high number of cases. There is, however, no evidence that this patient was devoted to horticulture or was exposed to externally noxious agents.

I shall discuss next a possible metabolic abnormality that might give rise to these difficulties. Aneurysms may occur when the elastic tissue of the media is faulty, and there are quite wide faults at the bifurcation of vessels very frequently. Yet elastic tissue is one of the toughest tissues in the body. Agents such as boiling oxalic acid or formic acid are required to dissolve it. Four years ago some Hungarian investigators[4] reported that they were able to isolate from the pancreas an elastase that would attack elastic tissue readily. This enzyme was not trypsin or chymotrypsin or carboxypeptidase. Of course, it would be unlikely, though possible, that polycystic disease of the pancreas allowed such enzymes, which normally should not be in the blood, to flow into the circulation, and it is difficult to imagine that these enzymes could concentrate in sufficient amounts in one area of the circle of Willis to produce an aneurysm. The finding of such an enzyme, however, raises the possibility of regulatory mechanisms in the body for elastic tissue. I shall have to leave that an open question.

The final group, which must be considered more seriously, is congenital malformations. That is not enough of an answer, however. If one tried to find the similarity between polycystic disease and aneurysm, one might postulate that an aneurysm is the nearest approach to a cyst that a blood vessel is capable of making, if it has a tendency to make a cyst. Another vascular disorder that does a better job of making cysts is congenital hemangiomas of both the brain and the retina, a combination known as Lindau–von Hippel disease. This disorder is characterized both by widely anastomosing channels and by the formation of extravascular cysts, which apparently result when the endothelial cells become isolated outside vessels and in some way stimulate the formation of small pockets of fluid. Lindau's disease, which is poorly understood, is also associated with polycystic kidneys, liver and pancreas. Consequently, I think we must consider that all three disorders — polycystic kidneys, congenital aneurysms and congenital hemangiomas — are probably manifestations of the same basic disorder.

In talking this over with Dr. Jerome Gross in the arthritis research unit, I was provided with an interesting hypothesis by which these two peculiar disorders might be integrated. Dr. Gross suggests the possibility that solid structures or organs form when the matrix, into which the cells migrate and multiply in embryonic life, is in a gelled state. If, for any reason, this matrix is fluid or becomes liquefied the cells have no framework on which to attach themselves and only thrive on the solid borders of this lake of fluid, thus producing a fluid-filled cavity. If more fluid is formed these pockets grow larger. Cyst formation may be attained on this basis. A comparable disorder in areas where elastic tissue should appear might prevent its formation (for it is possible that elastic fibers do not appear unless gelation of a ground substance has taken place). I think that as an overall principle I might speculate that embryologically there had been local failures of gelation, resulting in poor ground substance, in the same way that lathyrism ends up with poor ground substance. Perhaps lathyrism and polycystic renal disease are not so distantly related after all.

This lack of gelation is comparable to what happens when fresh pineapple juice, with its content of papain, is put in a gelatin dessert, which then remains liquid instead of solidifying into a gelled mass. Whatever the disorder was here, and whether these cases may eventually be traced to some toxic substance or a genetic dystrophy, I think the answer may be related to a better understanding of the factors that lead to better gelation.

DR. AUSTIN L. VICKERY: Dr. Benedict, would you like to comment on what you saw at peritoneoscopy?

DR. EDWARD B. BENEDICT: This patient, being a nurse at this hospital, was somewhat worried about the possibility of carcinoma of the liver. We believed the best way to rule that out was by peritoneoscopy. There were multiple cysts on the surface of the liver and also in the omentum and mesentery. The cysts had a bluish appearance that was probably due to hemorrhage. We believed that we had ruled out carcinoma.

DR. VICKERY: Dr. Culver, would you tell us what the opinion on the ward was?

DR. PERRY J. CULVER: Dr. Berg has speculated so brilliantly about the underlying nature of this disease that I think it would be interesting to add a contrapuntal theme. The story of the patient's social and economic life reads like a "soap opera." She had a psychopathic husband. She had a son whom she wanted to raise properly so she moved from the hospital area into the country, thereby adding stress to her life, for she worked at night and helped take care of the boy during the day. She was sure that she had cancer, so she decided to work as hard as she could during the remaining months left to her, to provide money for the son. When she finally decided that she was not dying with cancer as quickly as she thought she should she consented to peritoneoscopy. The episode that brought her into the emergency ward with pain in the abdomen was associated with a very unpleasant home situation. We thought at that time that one of the cysts in the abdomen had ruptured. Shortly after discharge from the hospital her husband was involved in an accident in which he was killed. Two days later the patient returned to work in spite of pain. On the morning of the final admission she was notified that the person driving the car with which her husband had collided was suing her for $10,000. I do not know what role these factors played in the

course of her disease, but I should like to add them to what Dr. Berg has put into the pot.

DR. VICKERY: I think the pot is full.

CLINICAL DIAGNOSES

Ruptured aneurysm of circle of Willis, with subarachnoid hemorrhage.
Polycystic disease of kidneys and liver.

DR. ROBERT L. BERG'S DIAGNOSES

Congenital aneurysm of circle of Willis, with rupture and subarachnoid and cerebral hemorrhage.
Polycystic kidney disease.

ANATOMICAL DIAGNOSES

Ruptured congenital aneurysm of circle of Willis, with subarachnoid hemorrhage.
Polycystic disease of kidneys and liver.

PATHOLOGICAL DISCUSSION

DR. VICKERY: It was obvious that this woman had the two disorders that Dr. Berg has so fully described. She died of a massive subarachnoid hemorrhage caused by rupture of an aneurysm at the approximate junction of the left anterior cerebral and anterior communicating artery.

The kidneys were huge, weighing together 2100 gm., or about six times the normal weight. The cortexes had a bosselated, cystic, multicolored appearance; on cut section, the cysts were seen to permeate the entire substance of both cortical and medullary portions of the parenchyma, with intervening islands of recognizable renal tissue. Both kidneys were similarly involved. The liver showed the same type of disease but not quite as strikingly as the kidneys. Polycystic disease of the liver, as Dr. Berg indicated, is a common accompaniment of congenital polycystic kidneys, occurring in about a third of the cases.

The etiology of polycystic disease is debatable. I think that all we can say about it and about multiple congenital anomalies in general is that there is some genetic basis for them. Dr. Castleman discussed it at one of these conferences in 1952.[5] The association of congenital polycystic disease and congenital aneurysm of the circle of Willis is well known. An analysis of a number of autopsies published about two years ago[6] showed that an intracranial aneurysm is found in about 1 per cent of all autopsies. Sixteen per cent of patients with polycystic kidneys, however, had intracranial aneurysms. The converse of this is that about 0.3 per cent of all autopsies show polycystic renal disease, but 4 per cent of patients with intracranial aneurysms have polycystic kidneys at autopsy. There is no doubt that there is a greater coincidence of these two disorders than chance alone would permit. The findings in this hospital are similar to the quoted statistics. Dr. Raymond A. Justi, the resident who performed this autopsy, has reviewed our autopsy experience with congenital polycystic kidneys and has found 23 cases — 19 adults and 4 infants. In 8 of these, there was associated polycystic disease of the liver; in none was there cystic disease of any other organ. Of 11 patients on whom brain examinations were performed, 2 had intracranial aneurysms. Last year Poutasse, Gardner and McCormack,[7] from the Cleveland Clinic, reported 3 cases of these two disorders that brought the total reported in the literature to 47. They also noted that the majority of patients with congenital polycystic kidney disease and intracranial aneurysms die of rupture of the aneurysm rather than of uremia from the congenital polycystic kidney disease.

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Correction. The citation of *Physiology* should be changed to *Angiology* in reference 8 on page 304 of the article by Imber and Clymer entitled "Obstruction of the Renal Artery Producing Malignant Hypertension," which appeared in the February 24 issue of the *Journal.*

The New England Journal of Medicine

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY

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THE FRUITS OF EXPLORATION

How to keep the balance between free exploration and protection for their young has been the problem of conscientious parents since the world began. Considering the constantly higher accident rate for males over females, it is doubtful whether man would ever have passed the Neanderthal stage if womankind had not constantly intervened to safeguard her own personal satisfactions and guarantee the future of the race. Now that mere survival from a host of infections is commonplace, it is disturbing to learn that accidents are the most frequent cause of death and disability before the age of thirty. Poisonings, which are a small proportion of this total, symbolize final frustration for adults and eager inquiry for the young.

Children begin their investigations at floor level and gradually expand their fields of interest from the kitchen cabinet to the drug closet in the bathroom. Kerosene and aspirin are their most fatal friends. Thereafter, chance and modern salesmanship determine what other hazards the young may encounter, from the latest perfume to the most effectively advertised pesticide.

Deaths from poisoning are four times as frequent in the United States as in the United Kingdom. One may conjecture why this is so, but at least the lack of oil-powered space heaters abroad and perhaps a less abundant distribution of the patented synthetic remedies reduce over there the juvenile hazards in which this country abounds.

The average American household is now equipped with a host of magic preparations, from detergents to exterminators, which find their way under the kitchen sink and are eagerly ingested. Labeling is often inadequate, and the solvents used are jealously guarded commercial secrets. All this can make life very difficult for the doctor called in to treat a case of childhood poisoning. Adults are more considerate. If they swallow something, it is usually with intent, and they are apt to reveal its nature.

Pediatricians have been increasingly concerned about the accident toll in childhood, and a Committee on Accident Prevention of the American Academy of Pediatrics has been active for nearly five years. The idea of maintaining central information points for the identification of poisons has gradually developed. Beginning over a year ago in Chicago several poison information centers have been developed. Washington and Boston have followed the example of Chicago.

The Boston Poison Information Center is located at the Children's Medical Center. It maintains a twenty-four-hour information service available to any physician who may be faced with the problem of treating a case of poisoning. This service, which has been developed with the sponsorship of the Massachusetts Chapter of the American Academy of Pediatrics, is a co-operative venture of the four teaching pediatric services in Boston. Details about the operation of the Center will be found in the announcement published

elsewhere in this issue of the *Journal*. It is hoped that community hospitals throughout the New England region will set up similar if less extensive services to the end that childhood poisonings may be given early and adequate treatment.

ATOM-POWERED PORTABLE X-RAY UNIT

In a release dated January 29, 1955, the Department of the Army announced the development of a portable x-ray unit, utilizing radioactive thulium as its source of radiation. A small amount of this substance encased in 0.6-cm. lead, which affords full protection to personnel, produces radiographs without the use of electricity, water or darkroom facilities. Radiosensitive paper separated from pads saturated in developer inside a leak-proof and light-proof cassette completes the equipment, which weighs only 48 pounds.

Thulium is a rare earth and, as thulium 170, emits gamma rays of 85-k.v. intensity. Its half life, of only 129 days, raises some doubt about the statement that the unit needs rejuvenation in an atomic pile but once a year. Whether the cost, $200, is for the unit itself, is surmised, since obtaining and processing thulium must entail considerable expense.

The true portability and simple operation will enable a medical corpsman to make the exposure timed by wrist watch and, by removing the cassette divider, to get the finished radiograph ready for inspection in five to ten minutes. Admittedly, the paper negatives produced lack the quality of conventional x-ray film, but they are suitable in such emergencies. Undoubtedly, further investigation will improve the process.

The atomic age moves on and with it the availability of instruments to ameliorate the lot of those wounded in combat. Although further tests and standardization will be necessary before these units become available commercially, there are many possible applications in civilian medicine, particularly civilian defense, to make this a worth-while addition to the medical armamentarium.

PROGRESS IN THE CHEMOTHERAPY OF TUBERCULOSIS

The Conferences on the Chemotherapy of Tuberculosis conducted by the Veterans Administration in collaboration with certain Army and Navy hospitals have established new landmarks in the search for a curative treatment of tuberculosis. Although the complex problems involved in this search have not yet been finally solved considerable progress toward that goal was reported at the fourteenth of these conferences, held in Atlanta, Georgia, February 7-10, 1955.

Among the most important contributions have been the definitive answers to specific and practical questions on therapeutic procedures that have been obtained by the collaborating investigators. This has been made possible by the recognition of the great importance of carefully controlled studies in patients selected at random within the limits of prearranged criteria, for well defined and specific purposes, and treated and studied in strict accordance with the protocols that the investigators themselves design and set up.

One of the specific answers brought out at this conference concerned the relative effectiveness of certain combinations of therapeutic agents in the treatment of pulmonary tuberculosis. The results obtained with any combination of streptomycin used twice weekly and isoniazid and para-aminosalicylic acid each used daily demonstrated no significant difference by any of the criteria used in the evaluations when the drugs were given in early cases, as original therapy (that is, in patients who had not previously received any of these antibiotics for their tuberculosis) and regardless of the degree and type of pulmonary involvement. The amount of benefit, however, depended on the severity of the disease when treatment was started, and the longer the treatment (these periods of study being as long as twelve months), the better the results. Moreover, the use of all three agents offered no particular advantage over that of any two of them as original therapy.

The number of patients in the controlled studies in which isoniazid alone was used were too few to be conclusive; the treatment appeared to be highly effective in early minimal cases of pulmonary tuberculosis, but did not seem to be desirable in far-advanced cases with very large cavities. Also, there still appears to be some doubt about the relative merits of streptomycin given daily as against twice a week when the more frequent doses are used for longer than a month and the total duration of treatment is longer than three months.

The striking effectiveness of the combination of isoniazid with pyrazinamide in both experimental and human infections, reported at the previous conference, was confirmed. However, the frequency of significant liver toxicity mentioned by different observers varied markedly, as did the interpretation of the positive liver-function tests observed with this combination of agents.

The results obtained in the treatment of miliary and meningeal tuberculosis have been particularly encouraging since isoniazid was introduced into the therapy. Ninety-five per cent of patients with miliary tuberculosis, but without meningitis, have survived for eighteen months with the use of isoniazid together with streptomycin, with or without para-aminosalicylic acid. In those with meningitis, with or without miliary disease, the mortality appears to be stabilized at approximately 20 per cent after eighteen months.

These figures for mortality and survival are much more favorable than those previously obtained with streptomycin and para-aminosalicylic acid or other combinations not utilizing isoniazid, and deaths continue to occur with such treatments after eighteen months. Moreover, meningitis has not been observed to develop for the first time in patients under treatment with isoniazid in combination with other agents for miliary tuberculosis; this often occurred with the earlier therapeutic regimens not using isoniazid, and survival in such cases was infrequent.

There has also been an encouraging drop in the amount of surgery, particularly pneumonectomy, deemed necessary in patients treated under the recent long-term regimens; fewer lobectomies are also being performed, and postoperative spreads of tuberculous infection of the lungs are occurring less often. Residual bronchopleural fistulas, however, are still frequent (6 per cent), regardless of the type of surgery. There is also a significant operative mortality, though not in cases of segmental resections, in which the mortality is very low. The question is now being asked whether the amount of surgery still being done is necessary and justified in patients receiving prolonged and adequate chemotherapy.

Equally favorable have been the results in a carefully followed series of cases of genitourinary tuberculosis in which treatment with combinations of agents, particularly those that include isoniazid, has been continued for at least a year. In this study, it has not been necessary to perform any nephrectomies or even partial resections of the kidneys. The patients who, according to previous indications, would have had such operations are being observed carefully; the kidneys show extensive scarring, but serious systemic vascular effects or diminution in renal function has not been encountered.

Other points of interest brought out in various papers and discussions at this conference are worth mentioning. A larger proportion of lungs resected after prolonged chemotherapy have shown viable and virulent tubercle bacilli as compared with those noted in earlier reports; the difference has been ascribed to more detailed and varied methods of culture, particularly prolonged incubation of washed specimens. All the factors involved, however, have not yet been defined, and differences of opinion concerning many of them still remain to be resolved. Observations on animal experiments have also been presented to substantiate earlier reports of loss of virulence in tubercle bacilli that have become resistant to isoniazid, but the significance of these findings in the infections of patients under treatment with this drug has not yet been established. Most of the highly resistant strains from human patients were found to have lost their ability to produce catalase, a property that has been considered to be associated with virulence. The importance of the metabolism of isoniazid in the body was also brought out, particularly the great individual variations in the proportion of the active drug in blood and tissues. The possibility of much larger doses than those presently recommended was suggested, but it was pointed out that pyridoxine in proper doses must be given along with the isoniazid to minimize the neurotoxicity that would otherwise accompany the use of such large doses.

The importance of histoplasmosis in the differential diagnosis or as a complication or concomitant infection in patients with pulmonary tuberculosis was also brought to the attention of the conference. This is particularly true in areas where histoplasmosis is endemic; in such areas more than 2 per cent of patients in tuberculosis sanatoriums can be demonstrated to have proved infection with both histoplasma and *Mycobacterium tuberculosis,* and more than 7 per cent have presumptive evidence of histoplasmosis by positive skin or complement-fixation tests.

The reports that received publicity in the lay press concerned the new antibiotic, cycloserine. This agent apparently has only low-grade activity in vitro against *M. tuberculosis* and many other common pathogens and exhibits no appreciable action on experimental tuberculosis in mice. Nevertheless, it was reported to have quite a favorable effect on active human pulmonary tuberculosis and also in certain other nontuberculous infections, notably those of the urinary tract. The enthusiasm accompanying these reports, however, was tempered by the evidence of certain toxic manifestations, particularly those involving the nervous system and perhaps also the kidney, which may be sufficiently serious and frequent to cause considerable concern about its uncontrolled use until these and other factors are properly studied in a much larger number of cases.

It is expected that details of the more important reports at this conference, particularly the data and interpretation of the results of the co-operative, controlled studies, will be published fairly soon. They should be of value to all physicians interested in the treatment of tuberculosis. The conferences themselves have proved highly stimulating to the workers in the participating hospitals, who have been attending them in increasing numbers and taking active parts in the programs and discussions. There can be little doubt that their patients benefit greatly from their participation and from the various other activities connected with these conferences.

ARS LONGA

A HALF millennium has passed since Leonardo made his anatomic sketches of the human body, and over four hundred years have fled since Calcar with his noble illustrations of Vesalius's *De humani corporis fabrica* introduced artistic accuracy to the more formal study of anatomy. Since that time medical illustration has revealed the possibilities not only of art in science but of science in art. Prior to

Calcar, except for Leonardo, much of medical art was grotesque and so was much of it for a long time afterward; but at least standards had been established.

Many of the present generation of somewhat older physicians, educated locally, will remember an instructor in surgical anatomy, at the blackboard, chalk in each hand, making skilful drawings in approximately half the time that the ordinarily able-bodied but single-handed artist would require; this exhibition of surgical ambidexterity represented but an incident in the steady progress of visual education. How far this progress has advanced and in how relatively short a time is illustrated by the rash promise of the first editors of the *New England Journal of Medicine and Surgery* who in 1812 committed themselves to the publication of at least one plate per volume, funds permitting.

The rapidity with which visual education has progressed has been due largely to photography and photoengraving, and to such mystery-laden devices as television, but nothing has as yet replaced the careful artist, capable of eliminating nonessential elements in the field and clearly portraying the points that are to be emphasized. Rapid as the advances in visual technology have been, the numbers and the training of good medical artists, and the need for them, have advanced as rapidly.

The tenth anniversary of the founding of the Association of Medical Illustrators and the publication by it of a new membership directory affords an opportunity to pay respect to this unique body of professional collaborators. Operating under their own code of ethics as essential partners in good medical publishing, the 107 active members of the Association, both here and abroad, have listed their names and qualifications over their own signatures, which is more than the owners of the names in most directories are given the opportunity of doing. The directory has been edited by a virtual dean of the country's medical illustrators, Muriel McLatchie Miller, director of the School of Medical Illustration and head of the Medical Art Department of the Massachusetts General Hospital.

Chloroform for Hiccough. — *I am not aware that it is generally known that chloroform is a specific for* hiccough. *I have used it for these last four years for checking it, and I have not failed in a single instance. A small quantity does, and I repeat it as often as the hiccough returns. Two or three applications generally prove successful.* — Dublin Medical Press, from Letter in Med. Cir.

Boston M. & S. J., April 12, 1855

MASSACHUSETTS MEDICAL SOCIETY

DEATH

CHAMP — Anthony M. Champ, M.D., of Brockton, died on February 12. He was in his sixty-third year.

Dr. Champ received his degree from Harvard Medical School in 1922. He was formerly president of the Brockton Medical Society.

BOSTON MEDICAL LIBRARY

NICOLAUS STENON

Nicolaus Stenon (1631-1687), a native of Copenhagen, was an eminent anatomist of the seventeenth century who studied under Thomas Bartholin and took his degree at Leyden. He traveled through Austria, Hungary and part of Italy, establishing himself in Florence, where, in 1667, he became physician to the Grand Duke Ferdinand II. In 1672 he was appointed professor of anatomy at the University in Copenhagen. In 1675 he gave up medicine for religion; he was later bishop of Heliopolis and wrote a number of controversial works on religious subjects. He is better known as the discoverer of the Stenon (parotid) duct. Recently, his letters *(Epistolae et epistolae ad eum datae. Qyas cum prooemio ac notis germanice scriptis. Edidit Gustav Scherz adjuvante Joanne Raeder)* were published in two sumptuous volumes. He was a many-sided man, anatomist, geologist and bishop.

CORRESPONDENCE

SEVERE, NOT MALIGNANT

To the Editor: I read with considerable interest the paper by Imber and Clymer, entitled "Obstruction of the Renal Artery Producing Malignant Hypertension," in the February 24 issue of the *Journal*. They reported that the ophthalmoscopic examination of their patient revealed Grade 3 Keith–Wagener hypertensive retinopathy.

Since the clinical criteria for the diagnosis of malignant hypertension include the papilledema characteristic of Grade 4 Keith–Wagener hypertensive retinopathy, as pointed out by Keith, Wagener and Kernohan *(Arch. Int. Med.* **41**:141-188, 1928), Derow and Altschule *(New Eng. J. Med.* **213**:951-960, 1935 and *Ann. Int. Med.* **14**:1768-1780, 1941), Pickering *(Circulation* **6**:599-612, 1952) and Schottstaedt and Sokolow *(Am. Heart J.* **45**:331-362, 1953), it is evident that the authors' use of the term *malignant* in describing the type of hypertension in their patient was incorrect. Their patient presented *severe* but not *malignant* hypertension.

HARRY A. DEROW, M.D.

Boston

NOTICES

BOSTON POISON INFORMATION CENTER

To help physicians in dealing with the problem of accidental poisoning, a Boston Poison Information Center has been established at the Children's Medical Center, 300 Longwood Avenue. This co-operative venture of the four pediatric teaching services in the city has been developed with the sponsorship of the Committee on Accident Prevention of the Massachusetts Chapter of the American Academy of Pediatrics, Dr. Henry E. Gallup, chairman. The Center is the third of its kind in this country. The others are located in Chicago and Washington, D.C.

Accidental poisoning in the young is often due to household substances whose nature is unknown to the physician on the case. Those finding themselves in difficulty are invited to call the Center at BEacon 2-2120 at any hour. The Center makes no claim to omniscience, but has sources of information that may be of help. There is no charge for this twenty-four-hour service unless long-distance telephone calls are necessary. These will be charged to the doctor requesting the service.

Those wishing further information may communicate with the Executive Secretary, Dr. Lendon Snedeker, at the Children's Medical Center. His telephone number is BEacon 2-7800.

This service is available to any physician. Lay inquirers will be referred to their family doctors.

SOUTH END MEDICAL CLUB

A meeting of the South End Medical Club of the Boston Tuberculosis Association will be held at the Veterans Administration Hospital, 150 South Huntington Avenue, Jamaica Plain, on Tuesday, April 26, at noon. Dr. Maurice B. Strauss will speak on the topic "Renal Failure."

Physicians are invited.

BOSTON UNIVERSITY SURGICAL SEMINAR

The Third (Boston University) Surgical Service, Boston City Hospital, will present the second annual surgical seminar on peripheral vascular disease in the Cheever Amphitheater, on Friday, April 22, from 9:30 a.m. to 4:30 p.m. Dr. Eugene E. O'Neil will be chairman.

The program is as follows:

9:30 a.m. Post-traumatic Sympathetic Dystrophy. Dr. George F. Miller, Boston University School of Medicine.

10:00 a.m. Clinicopathologic Course of Thromboangiitis: Therapeutic considerations. Dr. Henry Haimovici, Montefiore Hospital, New York City.

11:00 a.m. Transmetatarsal Amputation. Dr. George P. Whitelaw, Boston University School of Medicine.

11:30 a.m. Experiences with Vessel Substitution in Peripheral Vascular Diseases. Dr. William S. Dye, University of Illinois College of Medicine.

2:00 p.m. Segmental Femoropopliteal Arterial Occlusion Treated with Resection and Grafting. Dr. D. Emerick Szilagyi, Henry Ford Hospital, Detroit, Michigan.

2:30 p.m. Medical Management of Arterial Occlusive Disease. Dr. A. Wilbur Duryee, New York University.

3:30 p.m. Thrombophlebitis: A study of 748 cases. Dr. John J. Byrne, Boston University School of Medicine.

4:00 p.m. Studies in Venous Thrombosis. Dr. John A. McLachlin, University of Western Ontario Faculty of Medicine.

HAMPDEN DISTRICT MEDICAL SOCIETY

The annual meeting of the Hampden District Medical Society will be held at Rovelli's, 1396 Boston Road, Springfield, Massachusetts, on April 26 at 6:30 p.m.

MIDDLESEX WEST DISTRICT MEDICAL SOCIETY

The annual dinner meeting of the Middlesex West District Medical Society will be held at the Wayside Inn, Sudbury, on Wednesday, April 27, at 6:30 p.m. Mr. Basil Collins, vice-president, Old Colony Trust Company, will discuss the topic "The Doctor and His Estate."

AMERICAN HEART ASSOCIATION SCIENTIFIC SESSION

The annual meeting and scientific session of the American Heart Association will be held at the Jung Hotel, New Orleans, October 22-26.

Panels and the general assembly will follow the scientific session. Abstracts of papers to be presented should be submitted in duplicate to the Medical Director, American Heart Association, 44 East 23d Street, New York 10, New York, before July 1. Abstracts should be not more than 300 words in length and should summarize the results obtained and conclusions reached.

MILITARY DISTRICT OF WASHINGTON VACANCIES FOR PHYSICIANS

Openings for civilian physicians under United States Civil Service appointments are available in the Military District of Washington, D. C., at salaries ranging from $7040 to $9360 per year. Further information may be obtained from the Civilian Personnel Office, Military District of Washington, Washington 25, D. C.

AMERICAN CONGRESS OF PHYSICAL MEDICINE AND REHABILITATION

The spring session of the Eastern Section of the American Congress of Physical Medicine and Rehabilitation, New England Society of Physical Medicine, Section on Physical Medicine of the Medical Society of the County of Kings, New Jersey Society of Physical Medicine, New York Society of Physical Medicine and Pennsylvania Academy of Physical Medicine and Rehabilitation will be held at the Hotel Lenox, Boston, Massachusetts, on April 23, starting at 9:30 a.m.

There will be panels on general subjects and on hands, backs and the place of the general practitioner in physical medicine and rehabilitation. Physicians, other professional personnel and guests are welcome.

YALE MEDICAL SOCIETY

The Yale Medical Society and the Woodward Lecture Fund will present Dr. George W. Pickering, professor of medicine, St. Mary's Hospital Medical School, London, England, who will speak on the topic "The Concept of Essential Hypertension" in Fitkin Amphitheater, Yale—New Haven Medical Center, on Monday, April 25, at 8:15 p.m.

SOCIETY MEETINGS AND CONFERENCES

APRIL. Postgraduate Medical Institute. Page 451, issue of September 9.

APRIL–MAY. Sanitary Engineering Center Training Programs. Page 122, issue of July 15.

APRIL 7–9. Postgraduate Course in Obstetrics and Pediatrics. Page 329, issue of February 24.

APRIL 7–28. Consultation Clinics for Crippled Children in Massachusetts. Page 551, issue of March 31.

APRIL 8. Massachusetts Society for Research in Psychiatry. Page 679, issue of February 24.

APRIL 13. Chelsea Soldiers' Home. Page 329, issue of February 24.

APRIL 13. New England Surgical Society. Spring Meeting. Massachusetts Memorial Hospitals and Boston University School of Medicine.

APRIL 13–MAY 25. Labey Clinic Lectures. Page 461, issue of March 17.

APRIL 13–JUNE 15. Boston State Hospital. Psychiatry Seminars. Page 461, issue of March 17.

APRIL 14–MAY 26. Boston City Hospital. House Officers' Lectures. Page 509, issue of March 24.

APRIL 18. Hartford Medical Society. Page 289, issue of February 17.

APRIL 21 and 22. New York Academy of Medicine (Eastern States Health-Education Conference). Page 922, issue of November 25.

APRIL 22. Boston University Surgical Seminar. Notice above.

APRIL 23. Massachusetts State Society of Medical Technologists. Page 461, issue of March 17.

APRIL 25. American Congress of Physical Medicine and Rehabilitation. Notice above.

APRIL 25–29. Industrial Health Conference. Page 509, issue of March 24.

APRIL 25. Yale Medical Society. Notice above.

APRIL 25–30. American College of Allergists. Page 462, issue of March 17.

April 26. Hampden District Medical Society. Page 603.
April 26. Harvard Medical Society. Page 509, issue of March 24.
April 26. South End Medical Club. Page 603.
April 26. Alpha Omega Alpha Lecture. Page 554, issue of March 31.
April 27. Middlesex West District Medical Society. Page 603.
April 27–30. Instituto Nacional de Cardiología de México. Page 554, issue of March 31.
April 28–30. American Goiter Association. Page 329, issue of February 24.
April 30. State University College of Medicine at New York City. Page 289, issue of February 17.
April 30. Phi Delta Epsilon Fraternity. Graduate Club of Boston. Page 461, issue of March 17.
May 4 and 5. American Psychosomatic Society. Page 286, issue of August 12.
May 6–8. Student American Medical Association. Page 461, issue of March 17.
May 7. Middlesex South District Medical Society. Postgraduate Course. Page 758, issue of October 28.
May 13 and 14. American Association for Cleft Palate Rehabilitation. Page 461, issue of March 17.
May 13–15. American Academy of Dental Medicine. Page 554, issue of March 31.
May 17–19. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.
May 18–20. American College of Cardiology. Page 414, issue of March 10.
May 23–27. American Trudeau Society. Page 462, issue of March 17.
May 29–June 2. American Society of X-Ray Technicians. Page 553, issue of March 31.
June 1–3. American College of Chest Physicians. Page 553, issue of March 31.
June 5 and 6. American Board of Physical Medicine and Rehabilitation. Page 794, issue of November 4.
June 7–9. United States Public Health Service Medical-Officer Examinations. Page 509, issue of March 24.
June 21–25. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.
July, August and September. Beth Israel Hospital Course. Page 509, issue of March 24.
July 10–16. Congress of Nobel Prize Winners. Page 510, issue of March 24.
July 11–15. Symposium on Tuberculosis. Page 509, issue of March 24.
August 28–September 2. American Congress of Physical Medicine and Rehabilitation. Page 157, issue of January 27.
October 6–8. Academy of Psychosomatic Medicine. Page 509, issue of March 24.
October 22–26. American Heart Association. Scientific Session. Page 603.
October 23–27. American Institute of Dental Medicine. Page 414, issue of March 10.
November 6–13. Second International Congress of Allergology. Page 157, issue of January 27.
November 19–21. American Association of Blood Banks. 8th Annual Meeting. Palmer House, Chicago, Illinois.
November 29–December 2. Interim Session of the American Medical Association. Boston.

Calendar for the Week Beginning Thursday, April 14

Thursday, April 14
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:00 m. Thoracic Conference. The Use of Radioactive Gold for Lymphatic Metastases in Bronchogenic Carcinoma. Dr. Harrison Black. Main Amphitheater, Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*12:15–1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.
*4:00–5:00 p.m. Pediatric Seminar. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Auditorium, New England Deaconess Hospital.
*7:00 p.m. Boston City Hospital. House Officers' Association. Medical Physics and the Neo-Atomic Age. Dr. Otto Glasser. New Cheever Amphitheater, Dowling Building, Boston City Hospital.

Friday, April 15
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Dr. Proger and Staff. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–5:00 p.m. Child Psychiatry. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.

Saturday, April 16
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:30 a.m. Surgical Grand Rounds. Dr. Child and Staff. Stearns Auditorium, New England Center Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

Monday, April 18
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Pediatric Medical Surgical Rounds. Drs. Baty and Swenson. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Metabolism Conference. Dr. Schwartz. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:00 p.m. Surgical Pathology. Dr. MacMahon. Stearns Auditorium, New England Center Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. MacMahon. Stearns Auditorium, New England Center Hospital.
*8:30 p.m. Hartford Medical Society. Medical Aspects of Mitral Commissurotomy. Dr. Louis A. Soloff. Hunt Memorial Building, Hartford, Connecticut.

Tuesday, April 19
Holiday

Wednesday, April 20
*8:00 a.m. Combined Rounds. Massachusetts General Hospital.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Orthopedic Grand Rounds, Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*11:00 a.m. Boston State Hospital. Psychiatry Seminar. Reflections on the Concept of Maturity in Personality. Dr. Robert W. White. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Fluid and Electrolyte Balance. Dr. George Bell. Joslin Auditorium, New England Deaconess Hospital.

*Open to the medical profession.

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1. Boland, E. W., and Headley, N. E.: J.A.M.A. 148:981, Mar. 22, 1952.

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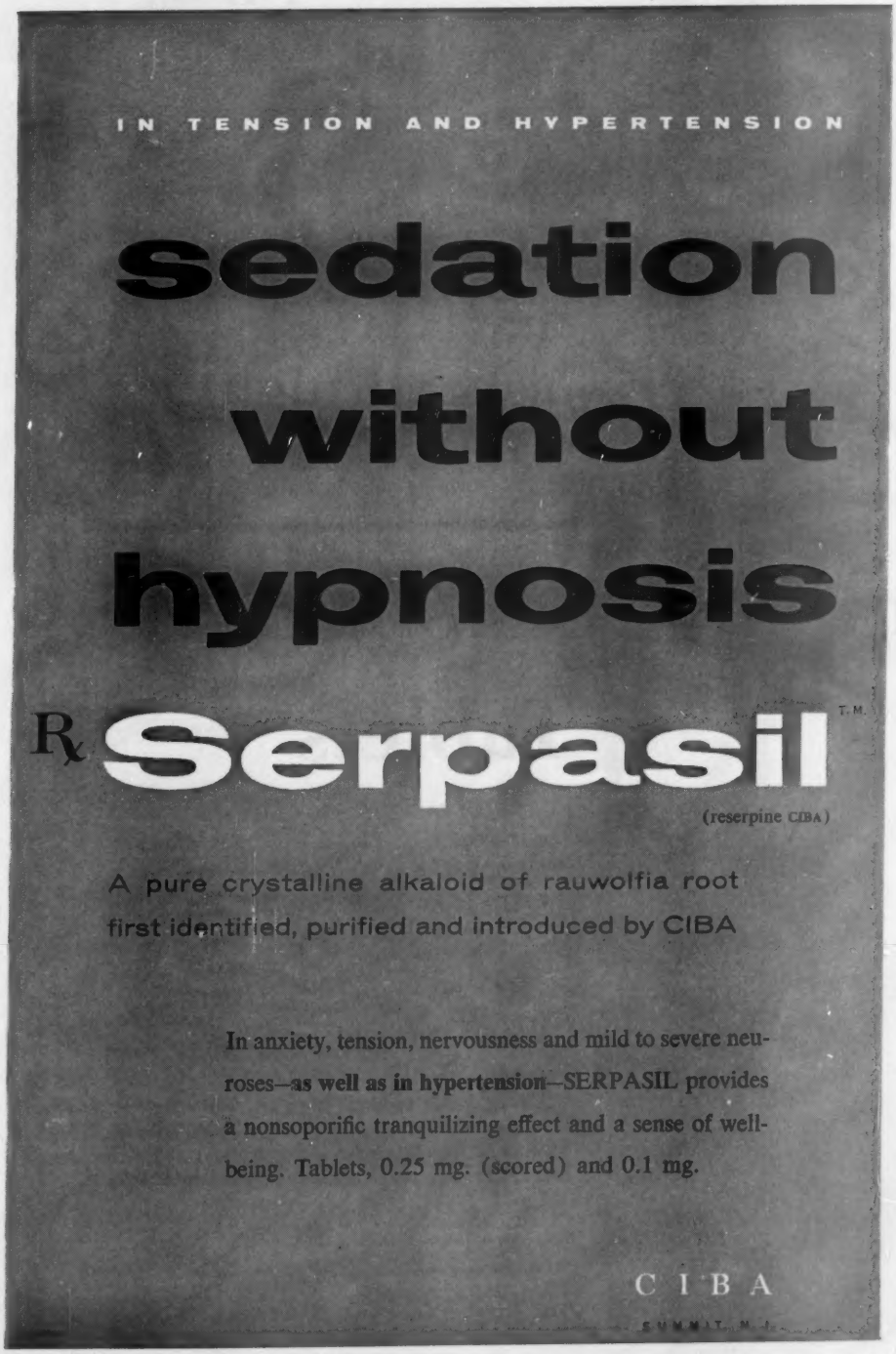
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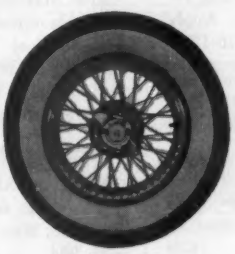

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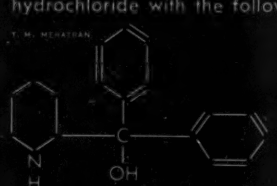

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1. Heath, R. C.: Discussion of paper by Howard D. Fabing (alpha-(2-piperidyl) benzhydrol hydrochloride, a new central stimulant in the treatment of blepharospasm, spasmodic torticollis and narcolepsy) presented before the American Neurological Association, Atlantic City, June 14, 1954. 2. Fabing, H. D., Hawkins, J. R., Moulton, J. A. L.: Clinical studies on alpha-(2-piperidyl) benzhydrol hydrochloride, a new antidepressant drug. Presented before the American Psychiatric Association, St. Louis, Missouri, May 3, 1954. 3. Fabing, H. D.: Alpha-(2-piperidyl) benzhydrol hydrochloride, a new central stimulant, in the treatment of blepharospasm, spasmodic torticollis and narcolepsy; preliminary report (Motion Picture Demonstration), American Neurological Association, June 14, 1954. 4. Himwich, H. E.: Discussion of paper (reference 2), American Psychiatric Association, May 3, 1954.

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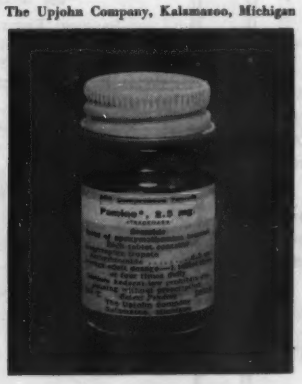

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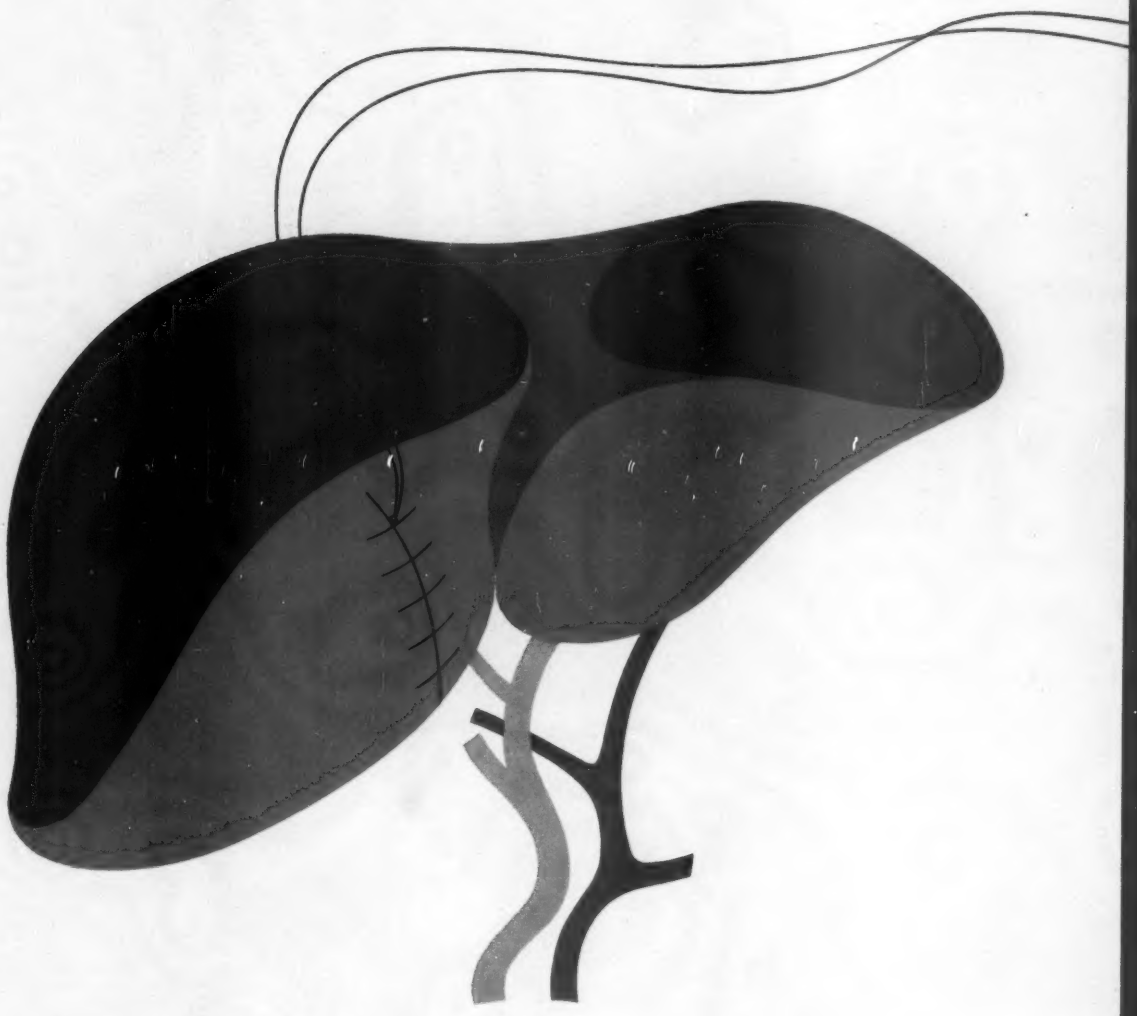

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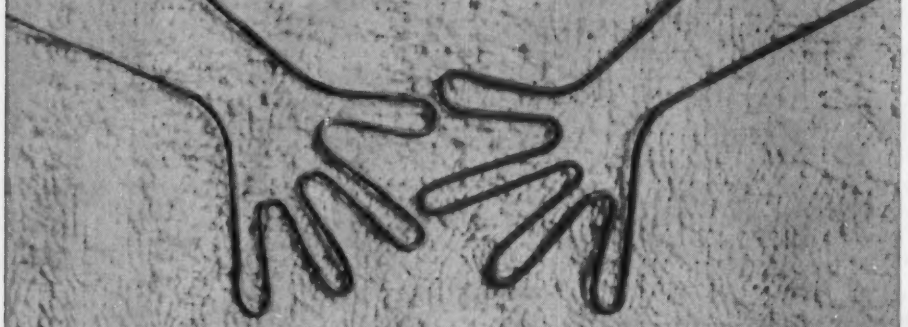

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